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(71) Applicant *(for all designated States except US)*: **MIKANA THERAPEUTICS** [US/US]; 6519 Dumbarton Circle, Fremont, CA 94555 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANANDAN, Sampath, K.** [IN/US]; 41069 Cornac Terrace, Fremont, CA 94539 (US). **XIAO, Xiao-Yi** [US/US]; 3851 Torrey Hill Lane, San Diego, CA 92130 (US). **PATEL, Dinesh, V.** [US/US]; 45109 Cougar Circle, Fremont, CA 94539 (US). **WARD, John, S.** [US/US]; 812 Corriente Pointe Drive, Redwood City, CA 94065 (US).

(74) Agent: **TODD, Stephen**; Foley & Lardner LLP, 1530 Page Mill Road, Palo Alto, CA 94304-1125 (US).

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(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: Disclosed are compounds which inhibit histone deacetylase (HDAC) enzymatic activity. Also disclosed are pharmaceutical compositions comprising such compounds as well as methods to treat conditions, particularly proliferative conditions, mediated at least in part by HDAC.

INHIBITORS OF HISTONE DEACETYLASE

CROSS-REFERENCE TO RELATED CASES

[001] This application claims the benefit under 35 U.S.C. §119(e) of United States Provisional Application Serial No. 60/551,644 filed March 8, 2004 and United States Application Serial No. 10/992,303, filed November 17, 2004, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[002] This invention relates to compounds which inhibit histone deacetylase (HDAC) enzymatic activity. This invention is also directed to pharmaceutical compositions comprising such compounds as well as to treat conditions, particularly proliferative conditions, mediated at least in part by HDAC.

References

[003] The following publications, patents and patent applications are cited in this application as superscript numbers:

[1] Marks, et al., Nature Reviews: Cancer 1:194-202 (2001)

[2] Finnin, et al., Nature, 401:188-193 (1999)

[3] Geerts, et al., European Patent Application Publication No. 0 827 742, published March 11, 1998

[004] All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

[005] In all eukaryotic cells, genomic DNA in chromatine associates with histones to form nucleosomes. Each nucleosome consists of a protein octamer made up of two copies of each histone: H2A, H2B, H3 and H4. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. The most common posttranslational modification of these core histones is the reversible acetylation of the ε-amino groups of conserved highly basic N-terminal lysine residues. The steady state of histone acetylation is established by the dynamic equilibrium between competing histone acetyltransferase(s) and histone deacetylase(s) herein referred to as HDAC.

[006] Histone acetylation and deacetylation has long been linked to transcriptional control. The recent cloning of the genes encoding different histone acetyltransferases and histone deacetylases provide a possible explanation for the relationship between histone acetylation and transcriptional control. The reversible acetylation of histones can result in chromatin remodeling and as such act as a control mechanism for gene transcription. In general, hyperacetylation of histones facilitates gene expression, whereas histone deacetylation is correlated with transcriptional repression. Histone acetyltransferases were shown to act as transcriptional coactivators, whereas deacetylases were found to belong to transcriptional repression pathways.

[007] The dynamic equilibrium between histone acetylation and deacetylation is essential for normal cell growth. Inhibition of histone deacetylation results in cell cycle arrest, cellular differentiation, apoptosis and reversal of the transformed phenotype. Therefore, HDAC inhibitors can have great therapeutic potential in the treatment of cell proliferative diseases or conditions.[1]

[008] The study of inhibitors of histone deacetylases (HDAC) indicates that indeed these enzymes play an important role in cell proliferation and differentiation. The inhibitor Trichostatin A (TSA) causes cell cycle arrest at

both the G1 and G2 phases, reverts the transformed phenotype of different cell lines, and induces differentiation of Friend leukemia cells and others. TSA (and suberoylanilide hydroxamic acid SAHA) have been reported to inhibit cell growth, induce terminal differentiation, and prevent formation of tumors in mice.[2]

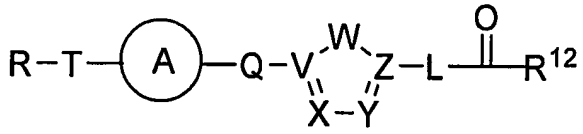
[009] Trichostatin A has also been reported to be useful in the treatment of fibrosis, e.g., liver fibrosis and liver chirrhosis.[3]

[0010] In view of the above, there is an ongoing need for inhibitors/antagonists of HDAC.

SUMMARY OF THE INVENTION

[0011] This invention provides compounds which inhibit HDAC activity and, accordingly, are useful as anti-proliferative agents in the treatment of proliferative diseases.

[0012] Accordingly, in one of its composition aspects, this invention is directed to a compound of formula I:



I

wherein:

R is selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkyl and substituted alkyl;

R^{12} is selected from the group consisting of $-NR^{14}OH$, -OH, $-NR^{14}R^{15}$, $-OR^{14}$, $-(C_1-C_6)$alkylene-SR^{14}, $-(C_1-C_6)$alkylene-OR^{14}, $-(C_1-C_6)$alkylene-$NR^{14}R^{15}$, $-CF_3$

where R^{14}, R^{15} are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)substituted alkyl, aryl, substituted aryl and where R^{14} and R^{15} together with the nitrogen atom bound thereto form a heterocyclic or substituted heterocyclic ring;

V, W, X, Y, and Z form a 5-membered heteroaryl where W, X, and Y independently form =C(R^{11})-, -N=, -N(R^{14})-, -O-, -S-, -S(O)-, and/or -S($O)_2$-, and V and Z independently form =C(R^{14})- and/or, >N- where R^{14} is as defined above and provided that at least one of V, W, X, Y and Z is =C(R^{14})-, and further provided that the 5-membered ring formed by V, W, X, Y, and Z is not a thienyl;

the ring defined by A above is selected from the group consisting of cycloakylene, substituted cycloalkylene, hetrocyclene, substituted heterocyclene, arylene and heteroarylene;

T is selected from the group consisting of -SO_2-[(C_1-C_3)alkylene]$_p$-, -[(C_1-C_3)alkylene]$_p$-SO_2-, -$NR^{16}SO_2$-[(C_1-C_3)alkylene]$_p$-, -SO_2NR^{16}-[(C_1-C_3)alkylene]$_p$-, -C(O)-[(C_1-C_3)alkylene]$_p$-, -[(C_1-C_3)alkylene]$_p$-C(O)-, -NR^{16}C(O)-[(C_1-C_3)alkylene]$_p$-, -C(O)NR^{16}-[(C_1-C_3)alkylene]$_p$-, -N(R^{16})-[(C_1-C_3)alkylene]$_p$ and (C_1-C_3)alkylene where *p* is zero or one and R^1 is hydrogen, alkyl, aryl or heteroaryl;

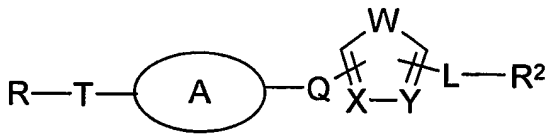
Q is selected from the group consisting of a covalent bond, (C_1-C_3)alkylene, -NR^1C(O)NR^1-, -NR^1C(O)-, -C(O)NR^1-, -(C_1-C_3-alkylene)$_p$$NR^1$- and -$NR^1$-($C_1$-$C_3$-alkylene)$_p$ where R^1 is hydrogen or alkyl and *p* is zero or one, provided that Q is not attached to X, Y or W when W is -O-, -S-, -S(O)-, -$S(O)_2$- and further provided that when Q is -NR^1- then Q is attached to a carbon atom of the ring defined by A above;

L is selected from the group consisting of a covalent bond, alkylene (C_1-C_4), substituted alkylene (C_1-C_4), alkenylene (C_2-C_4), and substituted alkenylene (C_2-C_4), cycloalkylene (C_3-C_8), and substituted cycloalkylene (C_3-C_8);

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

[0013] Preferred heteroaryl groups defined by V, W, X, Y and Z include furan, imidazole, pyrrazole, isoxazole, isothiazole, oxadiazole, thiazole, tetrazole, triazole, oxazole, pyrrole, thiadiazole, and the like. However, the instant invention does not encompass compounds in which V, W, X, Y and Z form a thienyl.

[0014] In another of its composition aspects, this invention is directed to a compound of formula Ia:



Ia

wherein:

R is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of $-C(O)NR^4R^5$, $-N(H)C(O)R^6$ $-C(O)(C_1-C_6)alkenylSR^6$, $NR^7C(O)N(OH)R^6$, $NR^7C(O)(C_1-C_6)alkenylSR^6$;

where R^4 and R^5 are independently selected from the group consisting of hydrogen, hydroxyl, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, and aminoaryl provided that both R^4 and R^5 are not hydroxyl;

R^6 is independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkylcarbonyl, aryl(C_1-C_6)alkyl, (C_1-C_6)alkylpyrazinyl, pyridinone, pyrrolidinone and methylimidazolyl; and

R^7 is independently selected from the group consisting of hydrogen, and (C_1-C_6)alkyl;

the ring defined by A above is selected from the group consisting of cycloalkylene, substituted cycloalkylene, heterocyclene and substituted heterocyclene;

T is selected from the group consisting of a bond, $-SO_2-[(C_1-C_3)alkylene]_p-$, $-NR^1SO_2-[(C_1-C_3)alkylene]_p-$, $-SO_2NR^1-[(C_1-C_3)alkylene]_p$, $-C(O)-[(C_1-C_3)alkylene]_p-$, $-NR^1C(O)-[(C_1-C_3)alkylene]_p-$, $-C(O)NR^1-[(C_1-C_3)alkylene]_p-$, and $(C_1-C_3)alkylene$ where *p* is zero or one and R^1 is hydrogen or alkyl;

W is selected from the group consisting of -O-, -S-, $-S(O)-$, $-S(O)_2-$ and $-NR^1-$ where R^1 is as defined above;

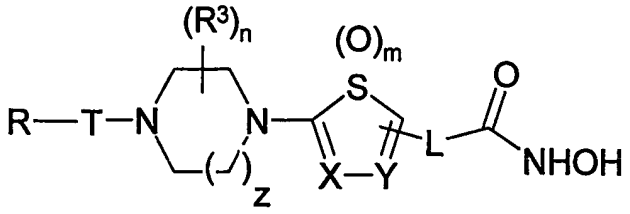
X and Y is selected from the group consisting of >CH and >N such that the 5 membered ring defined by W, X, Y and the two >CH groups is a heteroaryl ring, with the proviso that the ring is not a thienyl;

Q is selected from the group consisting of a covalent bond, $(C_1-C_3)alkylene$, $-NR^1C(O)NR^1-$, $-NR^1C(O)-$, $-C(O)NR^1-$, $-(C_1-C_3-alkylene)_pNR^1-$ and $-NR^1-(C_1-C_3-alkylene)_p$ where R^1 is hydrogen or alkyl and *p* is zero or one, provided that Q is not attached to X, Y or W when W is -O-, -S-, $-S(O)-$, $-S(O)_2-$ and further provided that when Q is $-NR^1-$ then Q is attached to a carbon atom of the ring defined by A above;

L is selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, and substituted alkenylene, cycloalkylene, and substituted cycloalkylene, provided that L is attached to a carbon atom of the 5 membered heteroaryl group;

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

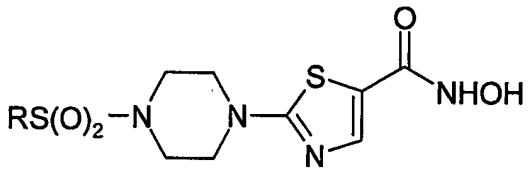
[0015] In one preferred embodiment, the compounds of this invention are represented by formula II:



II

where L, R, T, X and Y are as defined above; each R^3 is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl; *m, n* and *z*, are independently integers equal to zero, one or two; as well as tautomers, isomers, prodrugs, and pharmaceutically acceptable salts thereof.

[0016] In a preferred embodiment of the invention, the compound of formula II may be further described by formula XI:



XI

wherein:

R is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, amino, substituted amino, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof

with the proviso that R is not 4-aminophenyl.

[0017] In one embodiment, R is preferably aryl and more preferably is phenyl or naphthyl (e.g., 2-napthyl).

[0018] In another embodiment, R is preferably substituted aryl and more preferably, R is a substituted phenyl group selected from the group consisting of:

3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluroromethylphenyl, 3-trifluroromethylphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, 4-acetylphenyl, 4-[(N-morpholino)-methyl]phenyl, 4-[(N-pyrrolidinyl)methyl]phenyl, 4-(N,N-dimethylamino-methyl)phenyl, 5-(N,N-dimethylamino)naphthyl, 4-pyrrolind-1-ylphenyl, 4-acetamidophenyl, 4-methyl-2,3-dihydrobenzisoxazinyl, 2,3-dihydro-benzofuran-5-yl, 2,1,3-benzothiadiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-chlorophenyl, 2-chloro-6-methylphenyl, 3-chloro-2,5-dimethylphenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chlorophenyl, 3-cyanophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-fluorophenyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 5-fluoro-2-methylphenyl, 4-methyl-sulfonylphenyl, 2-methylphenyl, 3-methylphenyl, 3-hydroxymethylphenyl, 3-(N,N-dimethylaminomethyl)phenyl, 3-(pyrrolidin-1-yl)methylphenyl, 4-ethylphenyl, 4-methylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-*iso*-propylphenyl, 4-*n*-propylphenyl, *t*-butylphenyl, (4-pyrazol-1-yl)phenyl, 3-biphenyl, 4-biphenyl, 4-(3-N,N-dimethylaminomethylphenyl)phenyl, 4-(3-N,N-dimethylaminophenyl)phenyl, 4-[(3-pyrrolind-N-ylmethyl)-phenyl]phenyl, 4-[(N-morpholinocarbonyl)phenyl]phenyl, 4-(N,N-dimethyl-aminocarbonylphenyl)phenyl, 4-(4-fluorophenyl)phenyl, 4-(pyrid-4-yl)phenyl, 4-(3-chlorophenyl)phenyl, 4-(2-chlorophenyl)phenyl, 4-(3-fluorophenyl)-phenyl, 4-(2-furanyl)phenyl, 4-[2-(pyrrrolidin-N-ylmethyl)thien-3-yl]phenyl, 4-[5-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(4-methylpiperidin-1-yl)phenyl]phenyl, 4-[(3-(N-methyl-N-{2-N,N-dimethyleth-1-yl}aminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-ethylaminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-isopropyl}aminomethyl)phenyl]phenyl, 4-(methylsulfonamidophenyl)phenyl, 4-[1,3-(benzodioxol-5-yl)]phenyl, 4-(pyrimidin-5-yl)phenyl, 2-(2-methyl-

thiopyrimidin-4-yl)thien-5-yl, 4-[4-(acetamidophenyl)]phenyl, 4-(2-N,N-dimethylaminothien-3-yl)phenyl, and 4-(pyrid-3-yl)phenyl.

[0019] In another embodiment, R is preferably heteroaryl. Preferred heteroaryls include, by way of example, thien-2yl, pyrid-2-yl, pyrid-3-yl, and benzothiofuran-2-yl.

[0020] In another embodiment, R is preferably substituted heteroaryl. Preferred substituted heteroaryls include, by way of example, 3,5-di-methylisoxazol-4-yl, 2-(4-morpholino)pyrid-5-yl, and 2-phenoxypyrid-5-yl.

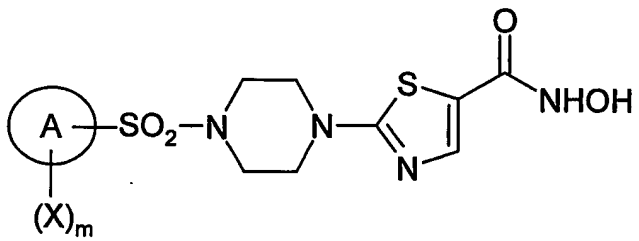
[0021] In another embodiment, R is preferably alkyl or substituted alkyl. Preferred alkyl and substituted alkyl include, by way of example, *n*-butyl, benzyl, and 2-phenylethyl.

[0022] In yet another embodiment, R is preferably alkenyl or substituted alkenyl. Preferred alkenyl and substituted alkenyl include, by way of example, *trans*-2-phenylethen-1-yl.

[0023] Still further, R is preferably amino or substituted amino such as dimethylamino.

[0024] Even still further, R is a substituted heterocyclic group such as 1-methyl-imidazol-4-yl.

[0025] Another preferred aspect of this invention is directed to compounds of formula XII:



XII

wherein:

A is selected from the group consisting of aryl and heteroaryl;

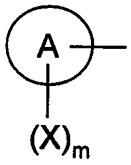
X is selected from the group consisting of acyl, acylamino, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, aminoacyl, aryloxy, substituted aryloxy, cyano, halo, heterocyclic, substituted heterocyclic, nitro, thioalkyl, substituted thioalkyl, and R^2-$S(O)_2(NH)_n$- where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

m is zero, one, two or three; and

n is zero or one;

with the proviso that -A-$(X)_m$ is not 4-aminophenyl.

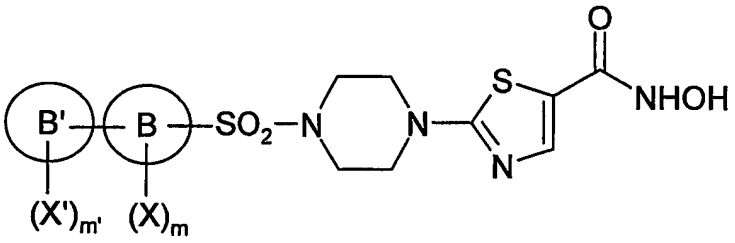
[0026] Preferred examples of substituents defined by the formula:



include by way of example only, phenyl, naphthyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-trifluoromethoxyphenyl, 2-triflurormethylphenyl, 3-triflurormethylphenyl, 4-triflurormethylphenyl, 4-nitrophenyl, 4-acetylphenyl, 4-[(N-morpholino)methyl]phenyl, 4-[(N-pyrrolidinyl)methyl]phenyl, 4-(N,N-dimethylaminomethyl)phenyl, 5-(N,N-dimethylamino)naphthyl, 4-pyrrolind-1-ylphenyl, 4-acetamidophenyl, 4-methyl-2,3-dihydrobenzisoxazinyl, 2,3-dihydrobenzofuran-5-yl, 2,1,3-benzothiadiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-chlorophenyl, 2-chloro-6-methylphenyl, 3-chloro-2,5-dimethylphenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chlorophenyl, 3-cyanophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-fluorophenyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 5-fluoro-2-methylphenyl, 4-methylsulfonylphenyl, 2-

methylphenyl, 3-methylphenyl, 3-hydroxymethyl-phenyl, 3-(N,N-dimethylaminomethyl)phenyl, 3-(pyrrolidin-1-yl)methylphenyl, 4-ethylphenyl, 4-methylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-*iso*-propylphenyl, 4-*n*-propylphenyl, *t*-butylphenyl, thien-2-yl, pyrid-2-yl, pyrid-3-yl, benzothiofuran-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(4-morpholino)pyrid-5-yl, and 2-phenoxypyrid-5-yl.

[0027] Another preferred aspect of this invention is directed to compounds of formula XIII as follows:



XIII

wherein:

B and B′ are independently selected from the group consisting of aryl and heteroaryl;

X and X′ are independently selected from the group consisting of acyl, acylamino, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, aminoacyl, aryloxy, substituted aryloxy, cyano, halo, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, nitro, thioalkyl, substituted thioalkyl, R^2-$S(O)_2(NH)_n$-, where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, and

m is zero, one, two or three;

m′ is zero, one or two; and

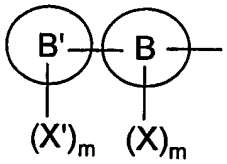
n is zero or one.

[0028] Preferably, *m* is zero and *m'* is one. When *m'* is one, X' is preferably substituted alkyl and more preferably is represented by the formula:

$$-CR^3R^4NR^5R^6$$

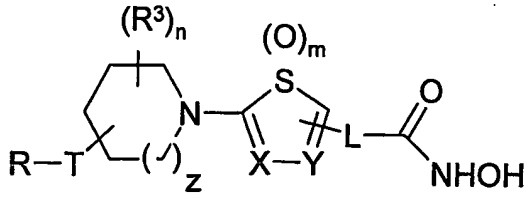
wherein R^3, R^4, R^5, or R^6 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl or R^5 and R^6 together along with N form a heterocylic or substituted heterocyclic ring containing 3-10 atoms.

[0029] Preferred examples of substituents defined by the formula:



include, by way of example only, (4-pyrazol-1-yl)phenyl, 3-biphenyl, 4-biphenyl, 4-(3-N,N-dimethylaminomethylphenyl)phenyl, 4-(3-N,N-dimethylaminophenyl)phenyl, 4-[(3-pyrrolind-N-ylmethyl)phenyl]phenyl, 4-[(N-morpholinocarbonyl)phenyl]phenyl, 4-(N,N-dimethylaminocarbonyl-phenyl)phenyl, 4-(4-fluorophenyl)phenyl, 4-(pyrid-4-yl)phenyl, 4-(3-chloro-phenyl)phenyl, 4-(2-chlorophenyl)phenyl, 4-(3-fluorophenyl)phenyl, 4-(2-furanyl)phenyl, 4-[2-(pyrrrolidin-N-ylmethyl)thien-3-yl]phenyl, 4-[5-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(4-methylpiperidin-1-yl)phenyl]phenyl, 4-[(3-(N-methyl-N-{2-N,N-dimethyleth-1-yl}aminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-ethylaminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-isopropyl)aminomethyl)phenyl]phenyl, 4-(methylsulfonamidophenyl)phenyl, 4-[1,3-(benzodioxol-5-yl)]phenyl, 4-(pyrimidin-5-yl)phenyl, 2-(2-methyl-thiopyrimidin-4-yl)thien-5-yl, 4-[4-(acetamidophenyl)]phenyl, 4-(2-N,N-dimethylaminomethyl-thien-3-yl)phenyl, and 4-(pyrid-3-yl)phenyl.

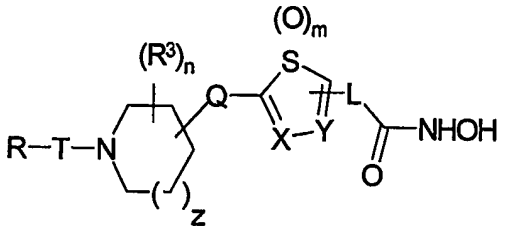
[0030] In another embodiment of the invention, the compounds of this invention are represented by formula III:



III

where *m*, *n*, *z*, L, R, R^3, T, X and Y are as defined above; as well as tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

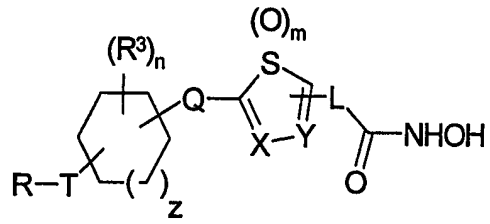
[0031] In still another embodiment, the compounds of this invention are represented by formula IV:



IV

where *m*, *n*, z, L, Q, R, R^3, T, X and Y are as defined above as well as tautomers, isomers, prodrugs, and pharmaceutically acceptable salts thereof.

[0032] In still another embodiment, the compounds of this invention are represented by formula V:



V

where *m*, *n*, z, L, Q, R, R^3, T, X and Y are as defined above as well as tautomers, isomers, prodrugs, and pharmaceutically acceptable salts thereof.

[0033] In one embodiment, R is preferably aryl and more preferably is phenyl or naphthyl (e.g., 2-napthyl).

[0034] In another embodiment, R is preferably substituted aryl and more preferably, 3,4-dimethoxyphenyl, 4-trifluoromethoxyphenyl, 4-methylphenyl. 4-triflurormethylphenyl, 4-nitrophenyl, 4-acetylphenyl, thiophen-2-yl, biphenyl, 5-(N,N-dimethylamino)-naphthalenyl, and 4-fluorophenyl.

[0035] In yet another embodiment, R is preferably alkyl or substituted alkyl, more preferably methyl, benzyl, 2-hydroxyethyl, 2-aminoethyl, and 2-phenylethyl.

[0036] In one embodiment, R^3 is alkyl and *n* is one. In another embodiment, *n* is zero.

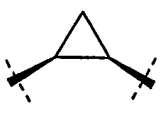
[0037] Preferably, *m* is zero.

[0038] In one embodiment, Q is a covalent bond and the ring defined by A above is piperidinyl. In still another embodiment, Q is a covalent bond and the ring defined by A above is piperazinyl.

[0039] X is preferably nitrogen and Y is preferably CH.

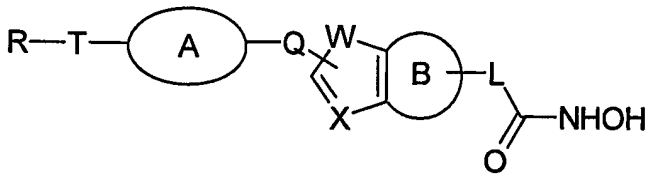
[0040] T is preferably selected from the group consisting of a bond, $-SO_2-$, and $-SO_2NH-$.

[0041] In one embodiment, L is a covalent bond. In another embodiment, L is an alkenylene group which is preferably ethenylene and more preferably *trans* (or Z) ethenylene. In still another embodiment, L is a cycloalkylene group, and more preferably cyclopropylene including *cis*-cyclopropylene and *trans*-cyclopropylene. In this application, cis-cyclopropylene (as well as cis-cycloalkylene) refers to the groups:

 and 

whereas trans-cyclopropylene (as well as trans-cycloalkylene) refers to the groups:

[0042] Still another class of compounds of this invention includes compounds of formula VI:



VI

where:

R is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

the ring defined by A above is selected from the group consisting of cycloalkylene, substituted cycloalkylene, heterocyclene and substituted heterocyclene;

T is selected from the group consisting of a bond, $-SO_2-[(C_1-C_3)alkylene]_p-$, $-NR^1SO_2-[(C_1-C_3)alkylene]_p-$, $-SO_2NR^1-[(C_1-C_3)alkylene]_p-$, $-C(O)-[(C_1-C_3)alkylene]_p-$, $-NR^1C(O)-[(C_1-C_3)alkylene]_p-$, $-C(O)NR^1-[(C_1-C_3)alkylene]_p-$, and $(C_1-C_3)alkylene$ where *p* is zero or one and R^1 is hydrogen or alkyl;

W is selected from the group consisting of -O-, -S-, $-S(O)-$, $-S(O)_2-$ and $-NR^1-$ where R^1 is as defined above;

X is selected from the group consisting of >CH and >N;

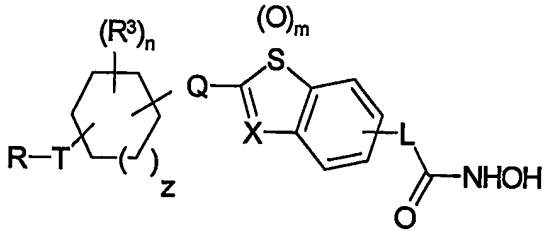
Q is selected from the group consisting of a covalent bond, $(C_1\text{-}C_3)$alkylene, $-NR^1C(O)NR^1-$, $-NR^1C(O)-$, $-C(O)NR^1-$, $-(C_1\text{-}C_3\text{-alkylene})_pNR^1-$ and $-NR^1-(C_1\text{-}C_3\text{-alkylene})_p$ where R^1 is hydrogen or alkyl and *p* is zero or one, provided that Q is not attached to X, Y or W when W is -O-, -S-, -S(O)-, $-S(O)_2-$ and further provided that when Q is $-NR^1-$ then Q is attached to a carbon atom of the ring defined by A above;

L is selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, cycloalkylene, and substituted cycloalkylene provided that L is attached to a carbon atom of the 5 membered heteroaryl group;

the cyclic structure defined by B, together with the unsaturation in the heteroaryl ring, is selected from the group consisting of cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, unsaturated heterocyclic and substituted unsaturated heterocyclic; and

and tautomers, isomers, prodrugs, and pharmaceutically acceptable salts thereof.

[0043] Particularly preferred compounds of formula VI include those of formula VII:



VII

where *m*, *n*, z, R, R^3, L, Q, T, and X are as defined above as well as tautomers, isomers, prodrugs, and pharmaceutically acceptable salts thereof.

[0044] In one of its pharmaceutical composition aspect, this invention is directed to a pharmaceutical composition comprising an effective amount of a

compound according to any of formulas I-VII, XI, XII or XIII and a pharmaceutically inert carrier.

[0045] In another of its pharmaceutical aspects, this invention is directed to pharmaceutical compositions comprising an effective amount of a compound according to any of formulas I-VII, XI, XII or XIII, an effective amount of at least one anti-cancer agent, and a pharmaceutically inert carrier.

[0046] In one of its method aspects, this invention is directed to a method for inhibiting a proliferative disorder in a mammalian patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I-VII, XI, XII or XIII or a mixture thereof.

[0047] In another of its method aspects, this invention is directed to a method for inhibiting a proliferative disorder in a mammalian patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier, an effective amount of at least one anti-cancer agent, and a therapeutically effective amount of a compound of formula I-VII, XI, XII or XIII or a mixture thereof.

[0048] In yet another of its method aspects, this invention is directed to a method for inhibiting a proliferative disorder in a mammalian patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I-VII, XI, XII or XIII or a mixture thereof in combination with at least one anti-cancer agent.

[0049] For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents. Examples of anti-cancer agents are: platinum coordination compounds for example cisplatin, carboplatin or oxalyplatin; taxane compounds for example paclitaxel or docetaxel; topoisomerase I inhibitors such as camptothecin

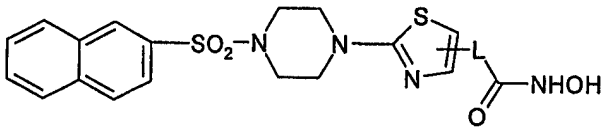
compounds for example irinotecan or topotecan; topoisomerase II inhibitors such as anti-tumour podophyllotoxin derivatives for example etoposide or teniposide; anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine; anti-tumor nucleoside derivatives for example 5-fluorouracil, gemcitabine or capecitabine; alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine or lomustine; anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin, idarubicin or mitoxantrone; HER2 antibodies for example trastuzumab; estrogen receptor antagonists or selective estrogen receptor modulators for example tamoxifen, toremifene, droloxifene, faslodex or raloxifene; aromatase inhibitors such as exemestane, anastrozole, letrazole and vorozole; differentiating agents such as retinoids, vitamin D and retinoic acid metabolism blocking agents (RAMBA) for example accutane; DNA methyl transferase inhibitors for example azacytidine; kinase inhibitors for example flavoperidol, imatinib mesylate or gefitinib; farnesyltransferase inhibitors; or other HDAC inhibitors.

[0050] In another of its method aspects, this invention is directed to a method for treating a mammalian patient with one or more diseases or disorders including hematological disorders, e.g., hemoglobinopathies (thalassemias, sickle cell anemias); autosomal dominant disorders, e.g., spinal muscular atrophy and Huntington's disease; genetic related metabolic disorders, e.g., cystic fibrosis and adrenoleukodystrophy; psoriasis; fibrosis, e.g., liver fibrosis, cirrhosis and fibrotic skin diseases, e.g., hypertrophic scars, keloid and Dupuytren's contracture; autoimmune diseases, e.g., systemic lupus erythematosus; acute or chronic degenerative conditions or diseases of the eye, e.g., glaucoma, dry age-related macular degeneration, retinitis pigmentosa and other forms of heredodegenerative retinal disease, retinal detachment and tears; macular pucker, ischemia affecting the outer retina, cellular damage associated with diabetic retinopathy and retinal ischemia, damage associated with laser therapy (grid, focal, and panretinal) including photodynamic therapy, trauma, surgical (retinal translocation, subretinal surgery, or vitrectomy) or light-

induced iatrogenic retinopathy, and preservation of retinal transplants; ocular neovascular or edematous diseases and disorders, e.g., diabetic retinopathy, rubeosis iritis, uveitis, Fuch's heterochromatic iridocyclitis, neovascular glaucoma, corneal neovascularization, neovascularization resulting from combined vitrectomy and lensectomy, retinal ischemia, choroidal vascular insufficinency, choroidal thrombosis, carotid artery ischemia, contusive ocular injury, retinopathy of permaturity, retinal vein occlusion, proliferative vitreoretinopathy, corneal angiogenesis, retinal microvasculopathy, or retinal eduema; connective tissue disease, e.g., rheumatoid arthritis, progressive systemic sclerosis, sjorgren's syndrome, dermatomyositis or mixed connective tissue disease; cardiac hypertrophy and heart failure; insulin resistance; amyotrophic lateral sclerosis; multiple sclerosis; Alzheimer's disease; neurodegenerative diseases; and lung diseases, e.g., cystic fibrosis, chronic obstructive pulmonary disease, asthma or acute and chronic bronchitis. Such methods comprise administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more compounds of formulas I-VII, XI, XII and/or XIII.

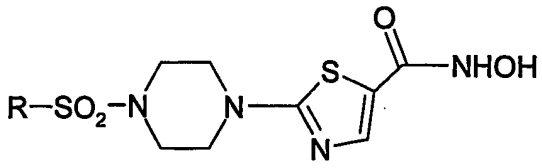
[0051] Preferred compounds of this invention include those found in the Tables below:

TABLE I



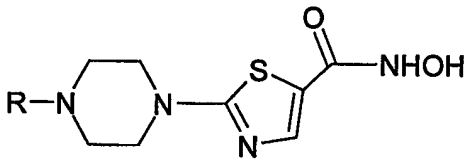
-L-C(O)NHOH
4-hydroxyaminocarbonyl
5-hydroxyaminocarbonyl
5-[(trans)-2-hydroxyamino-carbonylethen-1-yl

TABLE II



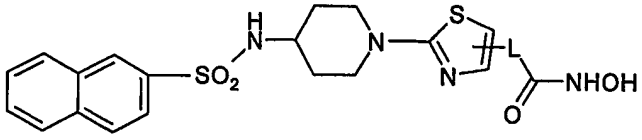
R
3,4-dimethoxyphenyl
4-trifluoromethoxyphenyl
4-methylphenyl
4-triflurormethylphenyl
4-nitrophenyl
4-acetylphenyl
thiophen-2-yl
biphenyl
5-(*N*,*N*-dimethylamino)-naphthalenyl
4-fluorophenyl

TABLE III



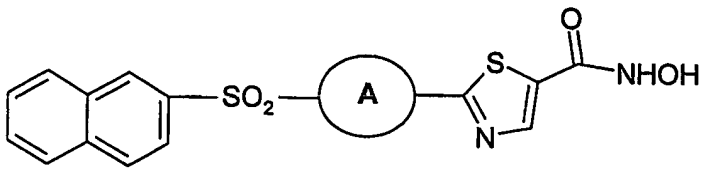
R
methyl
benzyl
2-hydroxyethyl
2-aminoethyl
2-phenylethyl

TABLE IV



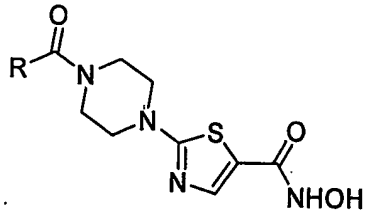
-L-C(O)NHOH
4-hydroxyaminocarbonyl

TABLE V



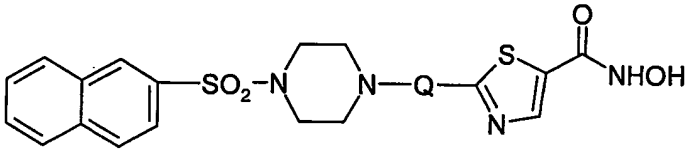
A
homopiperazinyl

TABLE VI



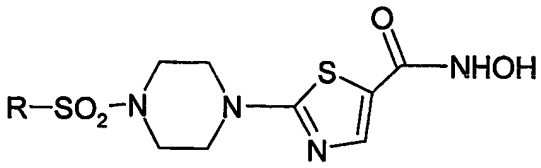
R
methyl
phenyl
benzyl

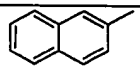
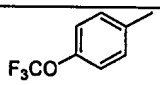
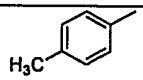
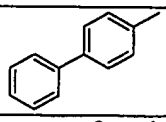
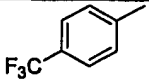
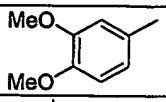
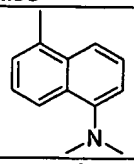
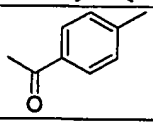
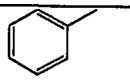
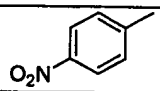
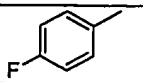
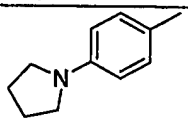
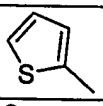
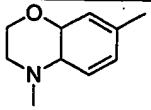
TABLE VII

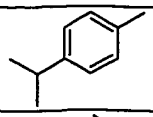
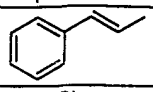
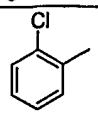
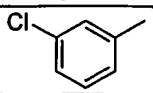
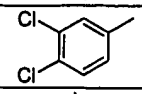
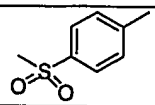
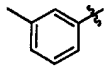
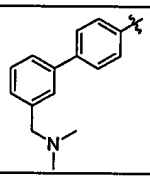
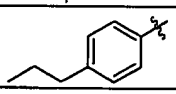
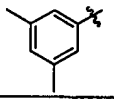
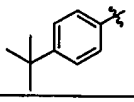
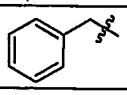
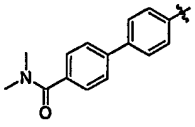
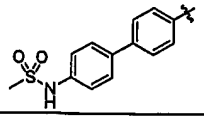
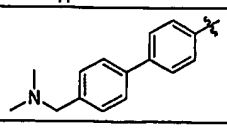


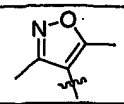
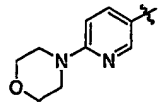
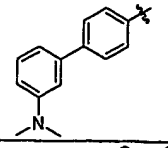
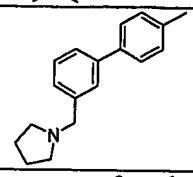
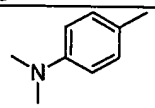
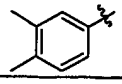
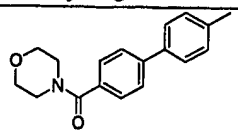
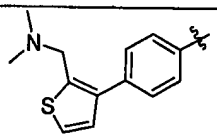
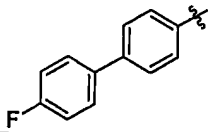
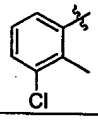
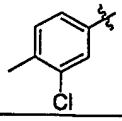
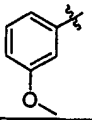
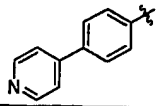
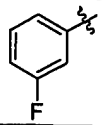
Q
methylene

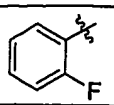
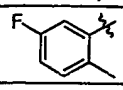
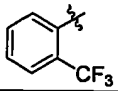
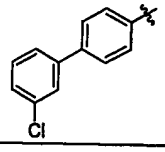
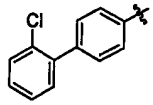
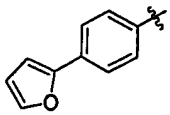
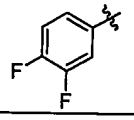
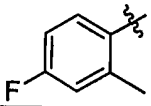
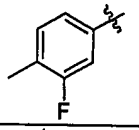
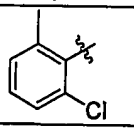
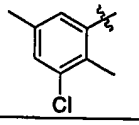
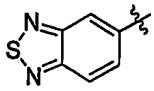
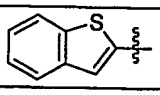
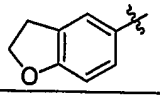
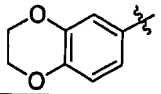
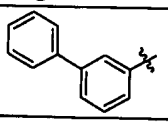
TABLE VIII

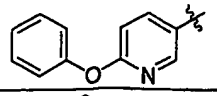
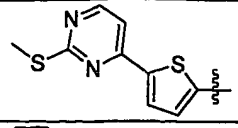
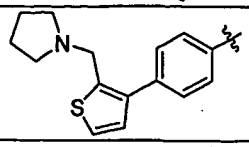
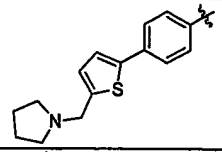
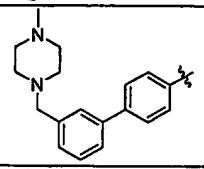
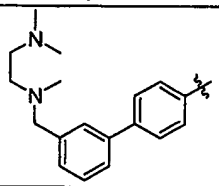
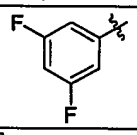
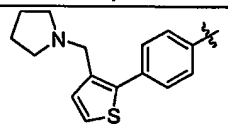
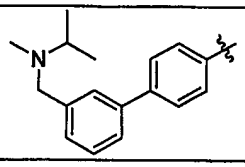
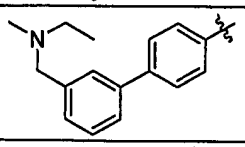
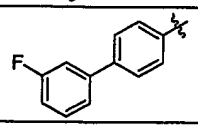
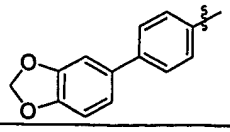
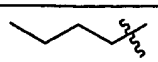


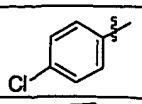
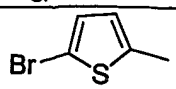
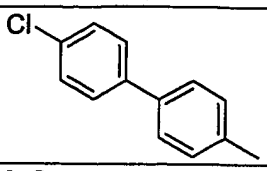
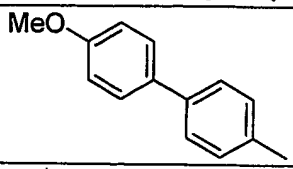
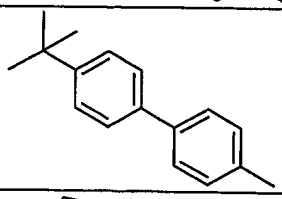
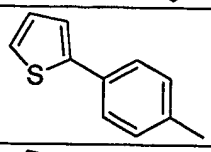
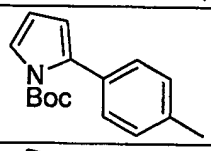
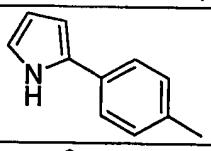
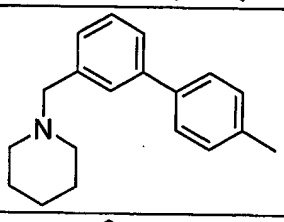
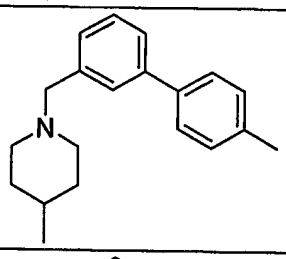
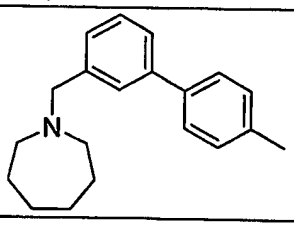
R	Name
	2-[4-(naphtha-2-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-pyrolidinylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(N-methyl-2,3-dihydrobenzisoxazinylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

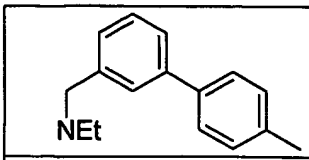
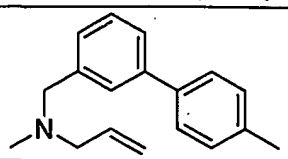
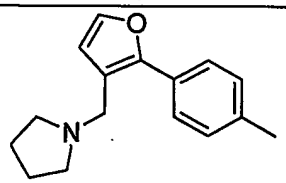
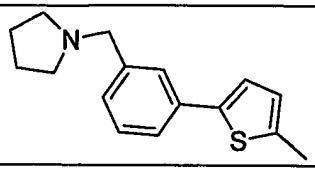
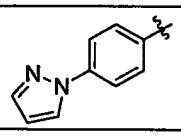
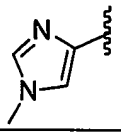
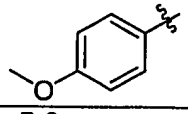
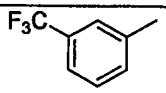
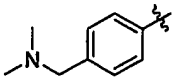
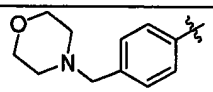
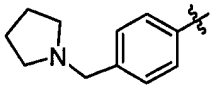
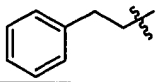
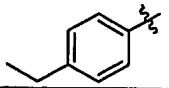
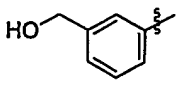
	2-[4-(4-*iso*propylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(*trans*-2-phenylethanelsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,4-dichlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(N,N-dimethylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-methylsufonylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(pyridine-3-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-[(dimethylamino)methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-*n*-propylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,5-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-t-butylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(benzylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4'-N,N-dimethylcarboxamido-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4'-methylsulfonylamino-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(4'-((dimethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

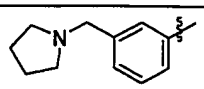
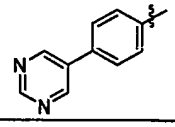
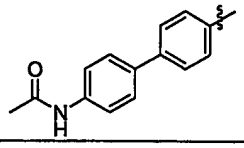
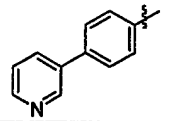
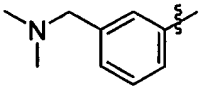
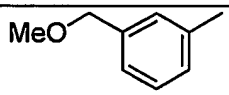
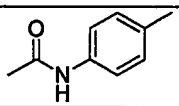
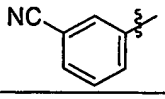
	2-[4-(3,5-dimethylisoxazolesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-({4-morpholino}-3-pyridylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3'-(dimethylamino)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-(pyrrolidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-dimethylaminophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,4-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4'-(morpholin-4-ylcarbonyl)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{4-[(2-((dimethylamino)-methyl)thien-3-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(4'-fluoro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-chloro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-chloro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[4-(pyridin-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

	2-[4-(2-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-methyl-5-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(2'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{[4-(2-furyl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,4-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-fluoro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-fluoro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-methyl-6-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2,5-dimethyl-4-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2,1,3-benzothiadiazole-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-benzothiphenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2,3-dihydrobenzofuransulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,4-benzodioxansulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-biphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

	2-[4-(2-phenoxypyridine-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(2-{2-methylthiopyrimidine-4-yl}-5-thiophenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-(4-[4-{(2-(pyrrolidin-1-ylmethyl)-thien-3-yl)phenylsulfonyl}]piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{4-[(5-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-((4-methylpiperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[3'-{[(2-(dimethylamino)ethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3,5-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-[isopropyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-[ethyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-fluoro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{[4-(1,3-benzodioxol-5-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(*n*-butylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

	2-[4-(chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(5-bromothien-2-yl)sulfonyl]piperazin-1-yl}-*N*-hydroxy-1,3-thiazole-5-carboxamide
	2-{4-[(4'-chloro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(4'-methoxy-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(4'-(2,2-dimethylpropyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(4-thien-2-ylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxamide
	2-(4-{[4-(1-(2,2-dimethylprop-oxycarbonyl)-1*H*-pyrrol-2-yl)phenyl]-sulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{[4-(1*H*-pyrrol-2-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-(piperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-(4-methylpiperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-(hexahydroazepin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

	2-{4-[(3'-((diethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(3'-((methyl(3-propenyl)amino)methyl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-(4-{5-[3-(pyrrolidin-1-ylmethyl)phenyl]thiophene-2-sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-pyrzaol-1-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-{1-methylimidazol-4-yl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-methoxyphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-{3-trifluoromethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-{N,N-dimethylaminomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-{N-morpholinomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-{N-pyrrolidinylmethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-phenethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-ethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-hydroxymethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

	2-[4-(3-pyrrolidin-1-ylmethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-pyrimid-5-ylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-{4-[(4'-(acetamidophenyl)-phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-pyridylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-{N,N-dimethylaminomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-methoxymethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(4-acetamido-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide
	2-[4-(3-cyanophenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

[0052] Particularly preferred compounds include the following compounds and pharmaceutically acceptable salts thereof:

1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl) piperazine;

1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl)-1,4-diazepane;

1-(2-naphthylsulfonyl)-4-(4-hydroxyaminocarbonylthiazol-2-yl) piperazine;

1-(2-naphthylsulfonyl)-4-[(5-(2-hydroxyaminocarbonylethen-1(Z)-yl-thiazol-2yl) piperazine;

4-(2-naphthylsulfonylamino)-1-[(5-(2-hydroxyaminocarbonyl-thiazol-2-yl)-piperadine;

2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-

carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4 toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-(4-methyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4- Benzyl -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-(2-hydroxyethyl)-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-(2-aminoethyl) -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-phenylethyl -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-acetyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide;

2-(4-benzoyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide;

2-(4-phenylacetyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide;

N-(2-naphthylsulfonyl)-N'-{2-[5-(N-hydroxycarboxamido)]thiazolyl}-

piperazine;

and pharmaceutically acceptable salts, isomers, tautomers, and prodrugs thereof.

2-[4-(naphtha-2-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-pyrolidinylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(thiophene-2-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(N-methyl-2,3-dihydrobenzisoxazinylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic

acid hydroxyamide;

2-[4-(trans-2-phenylethanelsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-dichlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(N,N-dimethylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-methylsufonylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(pyridine-3-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-[(dimethylamino)methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-n-propylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,5-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-t-butylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(benzylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4'-N,N-dimethylcarboxamido-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4'-methylsulfonylamino-1,1'-biphenylsulfonyl)piperazin-1-yl]-

1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-((dimethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,5-dimethylisoxazolesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-({4-morpholino}-3-pyridylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3'-(dimethylamino)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(pyrrolidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-dimethylaminophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4'-(morpholin-4-ylcarbonyl)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(2-((dimethylamino)-methyl)thien-3-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-fluoro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-chloro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-chloro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[4-(pyridin-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-methyl-5-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(2-furyl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-fluoro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-fluoro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-methyl-6-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2,5-dimethyl-4-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2,1,3-benzothiadiazole-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-benzothiphenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2,3-dihydrobenzofuransulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-benzodioxansulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-biphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-phenoxypyridine-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-{2-methylthiopyrimidine-4-yl}-5-thiophenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-(4-[4-{(2-(pyrrolidin-1-ylmethyl)-thien-3-yl)phenylsulfonyl}]-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(5-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-((4-methylpiperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(2-(dimethylamino)ethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,5-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-[isopropyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-[ethyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-fluoro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(1,3-benzodioxol-5-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(n-butylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(5-bromothien-2-yl)sulfonyl]piperazin-1-yl}-N-hydroxy-1,3-thiazole-5-carboxamide;

2-{4-[(4'-chloro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-methoxy-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-(2,2-dimethylpropyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4-thien-2-ylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxamide;

2-(4-{[4-(1-(2,2-dimethylprop-oxycarbonyl)-1H-pyrrol-2-yl)phenyl]-sulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(1H-pyrrol-2-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(piperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(4-methylpiperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(hexahydroazepin-1-ylmethyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-((diethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-((methyl(3-propenyl)amino)methyl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{5-[3-(pyrrolidin-1-ylmethyl)phenyl]thiophene-2-sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-pyrzaol-1-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{1-methylimidazol-4-yl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-methoxyphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-{3-trifluoromethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{N,N-dimethylaminomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{N-morpholinomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{N-pyrrolidinylmethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-phenethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-ethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-hydroxymethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-pyrrolidin-1-ylmethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-pyrimid-5-ylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-(acetamidophenyl)-phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-pyridylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-{N,N-dimethylaminomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-methoxymethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-acetamido-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-cyanophenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2-chloro-5-methoxyphenyl)sulfonyl]piperazin-1-yl}--1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[3-(difluoromethoxy)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4-methyl-3-nitrophenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2,5-dimethoxyphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2,5-dimethylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[2-(pyrrolidin-1-ylmethyl)-4-methylphenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[3-fluoro-4-(pyrrolidin-1-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(piperidin-1-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(morpholin-4-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(trifluoromethyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[ethylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[*N*-acetylamino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{methoxymethyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[4-(2-(pyrrolidin-1-ylmethyl)-thien-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[3-((dimethylamino)-methyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(4-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(3-((dimethylamino)methyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(2-hydroxyethyl)(methyl)amino]methyl}-1,1'-

biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[bis(2-hydroxyethyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-(3,6-dihydropyridin-1(2*H*)-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(butyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-((piperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(2-methoxyethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[bis(3-propenyl))amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[methylamino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[2'-{pyrrolidin-1-ylmethyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0053] As noted above, this invention is directed to compounds, pharmaceutical compositions and methods for inhibiting histone deacetylase (HDAC) enzymatic activity. However, prior to describing this invention in more detail, the following terms will first be defined.

Definitions

[0054] Unless otherwise limited by a specific recitation herein, the following terms have the following meanings;

[0055] "Alkyl" refers to monovalent alkyl groups having from 1 to 10 carbon atoms, preferably from 1 to 5 carbon atoms and more preferably 1 to 3 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl and the like.

[0056] "Substituted alkyl" refers to a monovalent alkyl group having from 1 to 3, and preferably 1 to 2, substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

[0057] "Alkylene" refers to divalent alkylene groups having from 1 to 10 carbon atoms, preferably from 1 to 5 carbon atoms and more preferably 1 to 3 carbon atoms. This term is exemplified by groups such as methylene, ethylene, *n*-propylene (1,3-propylene), *iso*-propylene (1,2-propylene), *n*-butylene (1,4-butylene), *n*-pentylene (1,5-pentylene), and the like.

[0058] "Substituted alkylene" refers to a divalent alkylene group having from 1 to 3, and preferably 1 to 2, substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

[0059] "Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *sec*-butoxy, *n*-pentoxy and the like.

[0060] "Substituted alkoxy" refers to the group "substituted alkyl-O-".

[0061] "Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O), heterocyclic-C(O)-, and substituted heterocyclic-C(O)-.

[0062] "Acylamino" refers to the group $-C(O)NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R^{10} is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring.

[0063] "Alkenyl" refers to a monovalent alkenyl group having from 2 to 6 carbon atoms and more preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. The term "alkenyl" encompasses any and all combinations of *cis* and *trans* isomers arising from the presence of unsaturation.

[0064] "Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic provided that any hydroxyl substitution is not on a vinyl carbon atom.

[0065] "Alkenylene" refers to a divalent alkenyl group having from 2 to 6 carbon atoms and more preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. The term "alkenylene" encompasses any and all combinations of *cis* and *trans* isomers arising from the presence of unsaturation.

[0066] "Substituted alkenylene" refers to alkenylene groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and

substituted heterocyclic provided that any hydroxyl substitution is not on a vinyl carbon atom.

[0067] "Amino" refers to the group $-NH_2$.

[0068] "Substituted amino" refers to the group –NR′R″ where R′ and R″ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where R′ and R″ are joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocylic group provided that R′ and R″ are both not hydrogen. When R′ is hydrogen and R″ is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R′ and R″ are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino.

[0069] "Aminoacyl" or "Acylamino" refers to the groups $-NR^{11}C(O)$alkyl, $-NR^{11}C(O)$substituted alkyl, $-NR^{11}C(O)$cycloalkyl, $-NR^{11}C(O)$substituted cycloalkyl, $-NR^{11}C(O)$alkenyl, $-NR^{11}C(O)$substituted alkenyl, $-NR^{11}C(O)$aryl, $-NR^{11}C(O)$substituted aryl, $-NR^{11}C(O)$heteroaryl, $-NR^{11}C(O)$substituted heteroaryl, $-NR^{11}C(O)$heterocyclic, and $-NR^{11}C(O)$substituted heterocyclic where R^{11} is hydrogen or alkyl.

[0070] "Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is to an aromatic ring atom. Preferred aryls include phenyl and naphthyl, e.g, 2-naphthyl.

[0071] "Substituted aryl" refers to aryl groups which are substituted with from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of hydroxy, acyl, acylamino, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, amino, substituted amino,

aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, carboxyl, carboxyl esters, cyano, cycloalkyl, substituted cycloalkyl, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, and substituted heterocyclyloxy.

[0072] "Aryloxy" refers to the group aryl-O- that includes, by way of example, phenoxy, naphthoxy, and the like.

[0073] "Substituted aryloxy" refers to substituted aryl-O- groups.

[0074] "Carboxyl" refers to –COOH or pharmaceutically acceptable salts thereof.

[0075] "Carboxyl esters" refers to the groups –C(O)O-alkyl, –C(O)O-substituted alkyl, –C(O)Oaryl, and –C(O)O-substituted aryl wherein alkyl, substituted alkyl, aryl and substituted aryl are as defined herein.

[0076] "Cycloalkyl" refers to monovalent cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple condensed rings which condensed rings may or may not be cycloalkyl provided that the point of attachment is to a cycloalkyl ring atom. Examples of cycloalkyl groups include, by way of example, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like.

[0077] "Substituted cycloalkyl" refers to a cycloalkyl group, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

[0078] "Cycloalkenyl" refers to monovalent cyclic alkenyl groups of from 4 to 10 carbon atoms, preferably 5 to 8 carbon atoms, having single or multiple

condensed rings which condensed rings may or may not be cycloalkenyl provided that the point of attachment is to a cycloalkenyl ring atom. Examples of cycloalkenyl groups include, by way of example, cyclopenten-4-yl, cycloocten-5-yl and the like.

[0079] "Substituted cycloalkenyl" refers to a cycloalkenyl group, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic provided that any hydroxyl substitution is not on an ethylenic carbon atom.

[0080] "Cycloalkylene" refers to divalent cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple condensed rings which condensed rings may or may not be cycloalkyl provided that the points of attachment are to cycloalkyl ring atoms. Cycloalkylene rings include, by way of example, cyclopropylene, 1,2-cyclobutylene, 1,3-cyclopentylene, 1,4-cyclooctylene, and the like. Cycloalkylene includes all *cis* and *trans* isomers encompassed by the particular cycloalkylene group.

[0081] "Substituted cycloalkylene" refers to a cycloalkylene group, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, amino, substituted amino, aminoacyl, aryl, substituted aryl, aryloxy, substituted aryloxy, cyano, halogen, hydroxyl, nitro, carboxyl, carboxyl esters, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

[0082] "Cycloalkoxy" refers to -O-cycloalkyl groups.

[0083] "Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

[0084] "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is fluoro or chloro.

[0085] "Heteroaryl" refers to a monovalent aromatic group of from 1 to 15 carbon atoms, preferably from 1 to 10 carbon atoms, and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, -S-, -SO-, and $-SO_2-$ within the ring. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl) provided that the point of attachment is through a heteroaryl ring atom. Preferred heteroaryls include pyridyl, pyrrolyl, indolyl, thiophenyl,and furyl.

[0086] "Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 3 substituents selected from the same group of substituents defined for substituted aryl.

[0087] "Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

[0088] "Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur, $-S(O)-$, $-S(O)_2-$, or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl provided that the point of attachment is to a heterocyclic (non-aromatic) ring atom.

[0089] "Substituted heterocyclic" refers to heterocyclic groups that are substituted with from 1 to 3 of the same substituents as defined for substituted cycloalkyl.

[0090] "Heterocyclene" refers to a divalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

[0091] "Substituted heterocyclene" refers to heterocyclene groups that are substituted with from 1 to 3 of the same substituents as defined for substituted cycloalkylene.

[0092] Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydro-isoquinoline, 4,5,6,7-tetrahydro-benzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

[0093] "Heterocyclyloxy" refers to the group -O-heterocyclic and "substituted heterocyclyloxy" refers to the group -O-substituted heterocyclic.

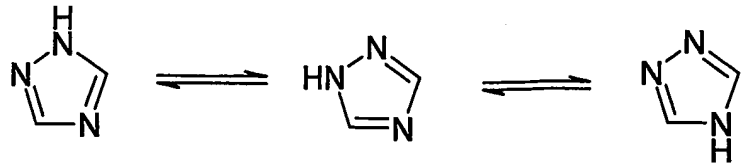
[0094] "Thioalkyl" refers to the group –S-alkyl.

[0095] "Substituted thioalkyl" refers to the group –S-substituted alkyl.

[0096] "Thienyl" refers to a 5-member heterocyclic ring comprising a single sulfur atom.

[0097] "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0098] "Tautomers" refers to structures which are art recognized to be in equilibrium with the depicted structure. For example, 1,2,4-imidazole has the following tautomeric structures:



all of which are art recognized.

[0099] The term "platinum coordination compound" is used herein to denote any tumor cell growth inhibiting platinum coordination compound which provides platinum in the form of an ion.

[00100] The term "taxane compounds" indicates a class of compounds having the taxane ring system and related to or derived form extracts from certain species of yew (Taxus) trees.

[00101] The term "topisomerase inhibitors" is used to indicate enzymes that are capable of altering DNA topology in eukaryotic cells. They are critical for important cellular functions and cell proliferation. There are two classes of topoisomerases in eukaryotic cells, namely type I and type II. Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight. The enzyme binds to DNA and introduces a transient single-strand break, unwinds the double helix (or allows it to unwind) and subsequently reseals the break before dissociating from the DNA strand. Topisomerase II has similar mechanism of action which involves the introduction of DNA strand breaks of the formation of free radicals.

[00102] The term "camptothecin compounds" is used to indicate compounds that are related to or derived from the parent camptothecin compound which is water-insoluble alkaloid derived from the Chinese tree Camptothecin acuminate and the Indian tree Nothapodytes foetida.

[00103] The term "podophyllotoxin compounds" is used to indicate compounds that are related to or derived from the parent podophyllotoxin, which is extracted from the mandrake plant.

[00104] The term "anti-tumour vinca alkaloids" is used to indicate compounds that are related to or derived from extracts of the periwinkle plant (*Vinca rosea*).

[00105] The term "alkylating agents" encompass a divers group of chemicals that have the common feature that they have the capacity to contribute, under physiological conditions, alkyl groups to biologically vital macromolecules such as DNA. With most of the more important agents such as the nitrogen mustards and the nitrosoureas, the active alkylating moieties are generated *in vivo* after complex degradative reactions, some of which are enzymatic. The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation in particular DNA synthesis and cell division. The capacity of alkylating agents to interfere with DNA function and integrity in rapidly proliferating tissues provides the basis for their therapeutic applications and for many of their toxic properties.

[00106] The term "anti-tumour anthracycline derivatives" comprise antibiotics obtained from the fungus *Strep. peuticus var. caesius* and their derivatives, characterized by having a tetracycline ring structure with an unusual sugar, daunosamine, attached by a glycosidic linkage.

[00107] Amplification of the human epidermal growth factor receptor 2 protein (HER 2) in primary breast carcinomas has been shown to correlate with a poor clinical prognosis for certain patients. Trastuzumab is highly purified recombinant DNA-derived humanized monoclonal IgG1 kappa antibody that binds with high affinity and specificity to the extracellular domain of the HER2 receptor.

[00108] Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogen. The terms "estrogen receptor antagonists" and "selective estrogen receptor modulators" are used to indicate competitive inhibitors of estradiol binding to the estrogen receptor (ER). Selective estrogen receptor modulators, when bound to the ER, induces a change in the three-dimensional shape of the receptor, inhibiting its binding to the estrogen responsive element (ERE) on DNA.

[00109] In postmenopausal women, the principal source of circulating estrogen is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition or inactivation is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer.

[00110] The term "antiestrogen agent" is used herein to include not only estrogen receptor antagonists and selective estrogen receptor modulators but also aromatase inhibitors as discussed above.

[00111] The term "differentiating agents" encompass compounds that can, in various ways, inhibit cell proliferation and induce differentiation. Vitamin D and retinoids are known to play a major role in regulating growth and differentiation of a wide variety of normal and malignant cell types. Retinoic acid metabolism blocking agents (RAMBA's) increase the levels of endogenous retinoic acids by inhibiting the cytochrome P450-mediated catabolism of retinoic acids.

[00112] DNA methylation changes are among the most common abnormalities in human neoplasia. Hypermethylation within the promoters of selected genes is usually associated with inactivation of the involved genes. The term "DNA methyl transferase inhibitors" is used to indicate compounds that act through pharmacological inhibition of DNA methyl transferase and reactivation of tumour suppressor gene expression.

[00113] The term "kinase inhibitors" comprises potent inhibitors of kinases that are involved in cell cycle progression and programmed cell death (apoptosis).

[00114] The term "farnesyltransferase inhibitors" is used to indicate compounds that were designed to prevent farnesylation of Ras and other intracellular proteins. They have been shown to have effect on malignant cell proliferation and survival.

Compound Preparation

[00115] The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[00116] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

[00117] Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless

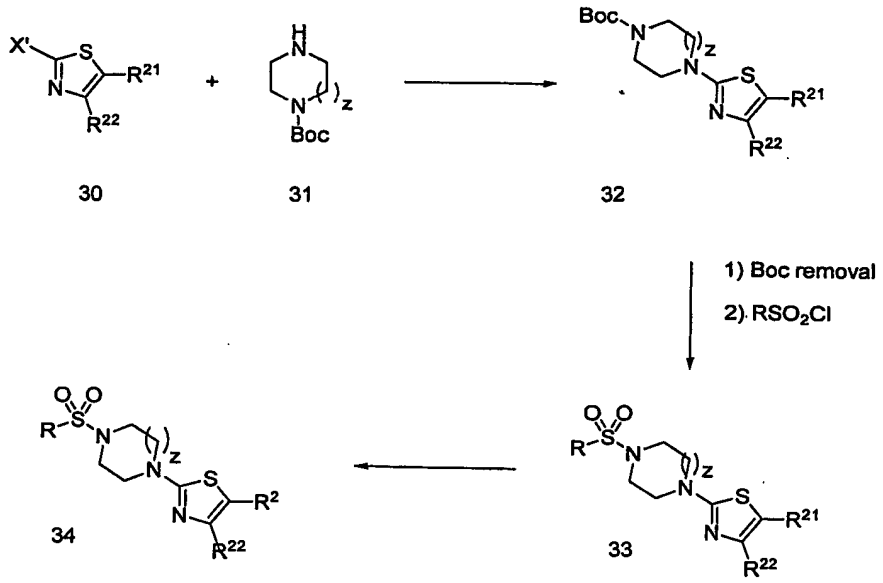
otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

[00118] Still further, some of the compounds defined herein include vinyl groups which can exist in *cis, trans* or a mixture of *cis* and *trans* forms. All combinations being within the scope of this invention.

[00119] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00120] As to the synthesis of compounds of this invention, Scheme 1 below illustrates a general method for synthesis wherein L is a covalent bond, X is N and Y is CH, and the ring defined by A contains two ring amino groups.

Scheme 1



where X' is a halogen such as bromo or chloro, one of R^{21} and R^{22} is -C(O)OPg where Pg is a carboxyl protecting group such as an alkyl group, e.g., methyl and the other is hydrogen, and R, R^2 and *z* are as defined above. For illustrative purposes in the discussion below, *z* will be assigned the value 1, R^{21} will be carboxy methyl ester (-$COOCH_3$), and R^{22} will be hydrogen. It is understood, of course, that other diaminoheterocycles such as where *z* is zero or two and other thiazole compounds can similarly be employed.

[00121] Specifically, commercially available methyl 2-halo-5-carboxylthiazole, compound 30, is condensed with at least an equivalent and preferably and excess of mono-protected 1-*t*-butoxycarbonyl (Boc) piperazine, compound 31, under conventional conditions to provide for methyl 2-[(1-t-butoxycarbonyl)piperazin-4-yl]-5-carboxylthiazole, compound 32. The reaction is typically conducted in an inert solvent such as acetonitrile, chloroform, and the like in the presence of a suitable base such as potassium carbonate which scavenges the acid generated during the reaction. The reaction is typically conducted at an elevated temperature of from about 40° to

100°C for a period of time sufficient for substantial completion of the reaction which typically occurs within about 2 to 48 hours. The resulting product, compound 32, can be recovered by conventional methods, such as chromatography, filtration, crystallization, evaporation and the like or, alternatively, used in the next step without purification and/or isolation.

[00122] Conventional deprotection of the Boc-protected amino group (e.g., TFA) of methyl 2-[(1-t-butoxycarbonyl)piperazin-4-yl]-5-carboxylthiazole, compound 32, provides for the corresponding methyl 2-(piperazin-4-yl)-5-carboxylthiazole, not shown, which is then reacted with a suitable sulfonyl chloride (RSO_2Cl) to provide for the corresponding sulfonyl amide, compound 33. This latter reaction is typically conducted by combining preferably from about 1.5 to about 2.5 equivalents, of the sulfonyl chloride in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about 0°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, N-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting N-sulfonyl amino acid, compound 33 is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, evaporation and the like.

[00123] The sulfonyl chlorides employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, i.e., from compounds of the formula RSO_3H where R is as defined above, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent,

such as dichloromethane, at temperature in the range of about 0 to about 80°C for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the sulfonyl chlorides can be prepared from the corresponding thiol compound, i.e., from compounds of the formula R-SH where R is as defined herein, by treating the thiol with chlorine (Cl_2) and water under conventional reaction conditions.

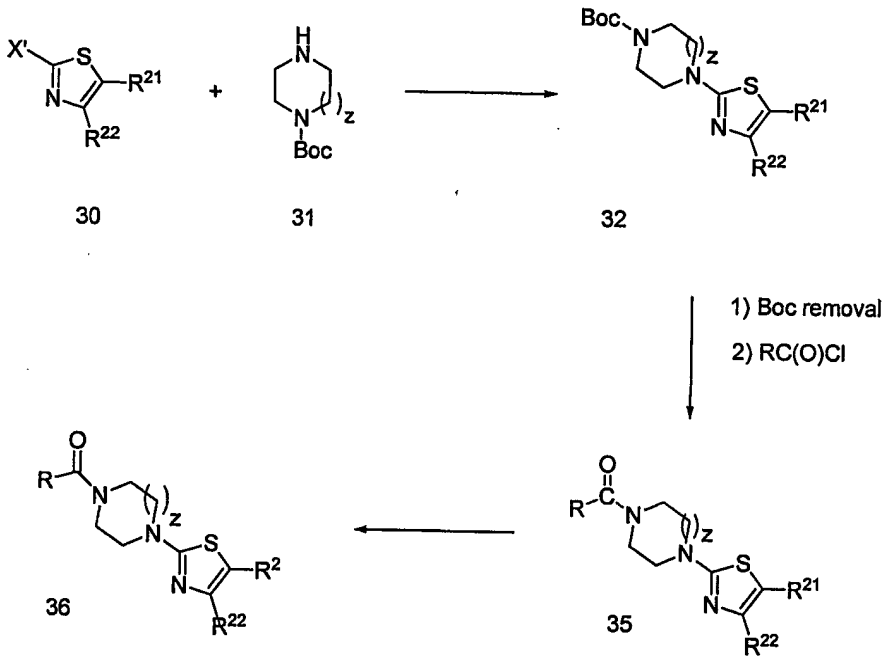
[00124] Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, p-toluenesulfonyl chloride, .2-methylphenylsulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-tert-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethyl-benzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the N-sulfonyl amino acids.

[00125] The R^{21} methyl carboxyl group of compound 33 can then be converted to a variety of amides including hydroxyamides by reaction with a 2-20 fold excess of a suitable amine such as hydroxylamine. The reaction is

typically conducted in a suitable diluent such as a 5:2 mixture of methanol to water under basic conditions, e.g, the addition of sodium hydroxide. The reaction is typically conducted at a temperature of from about -20° to 20°C for a period of time sufficient for substantial completion of the reaction which typically occurs within about 0.5 to 10 hours. The resulting amide, compound 34, can be recovered by conventional methods, such as chromatography, filtration, crystallization, evaporation and the like.

[00126] Scheme 2 illustrates the synthesis of compounds of formula I where T is a carbonyl group.

Scheme 2



where R, R^2, R^{21}, R^{22}, Boc, X' and *z* are as defined above.

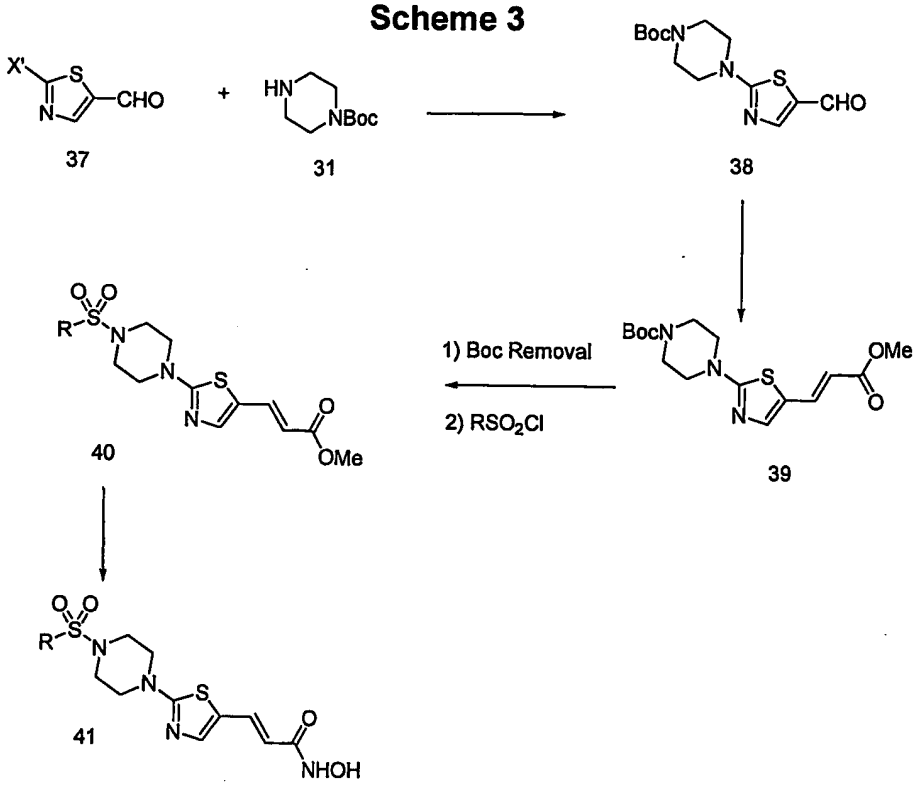
[00127] Specifically, in Scheme 2, compound 32 is prepared as per Scheme 1 above. Conventional removal of the Boc group provides for the free amino group on the piperazine ring (not shown). The amino group is then acylated by conventional means such as reaction with an excess of the acid chloride,

RC(O)Cl, in a suitable inert diluent such as dichloromethane and preferably in the presence of an tertiary amine to scavenge the acid generated during the reaction. The resulting amide, compound 35, can be recovered by conventional methods, such as chromatography, filtration, crystallization, evaporation and the like. Conversion of amide 35 to compound 36 proceeds in the manner described above.

[00128] In Schemes 1 and 2, replacement of 4-Boc-piperazine with mono-amino protected diamino compounds provides for compounds of formula I such as those where Q is amino, T is a sulfonylamide, etc. Examples of commercially available diamino compounds include 1,4-diaminocyclohexane, 1,2-diaminocyclohexane, 4-aminopiperidine, 3-aminopiperidine, 3-aminopyrrolidine, 4-(aminomethyl)piperidine, 2-(aminomethyl)pyrrolidine, and the like. These compounds can be conventionally mono-amino protected to provide for suitable reagents for use in this invention.

[00129] Scheme 3 illustrates the synthesis of compounds of formula I where L is an alkenylene group.

Scheme 3



where X', R and Boc are as defined above.

Specifically, commercially available 2-bromo-5-formylthiazole, compound 37, is condensed with at least an equivalent and preferably and excess of mono-protected 1-*t*-butoxycarbonyl (Boc) piperazine, compound 31, as described above to provide for methyl 2-[(1-t-butoxycarbonyl)piperazin-4-yl]-5-formylthiazole, compound 38. Alternatively, 2-bromo-5-formylthiazole can be prepared from the 5-carboxyl precursor, compound 30 where R^{21} is carboxyl or a carboxyl ester, by conventional reduction procedures.

[00130] Conversion of compound 38 to compound 39 proceeds via a conventional Wittig Horner reaction.

[00131] Removal of the Boc protecting group proceeds via conventional conditions to provide for the free amine, not shown, which is then contacted with an excess of sulfonyl chloride in the manner described above to provide for compound 40. Conversion of the methyl ester of compound 40 to the corresponding amide, e.g., hydroxylamide, proceeds via contacting the ester

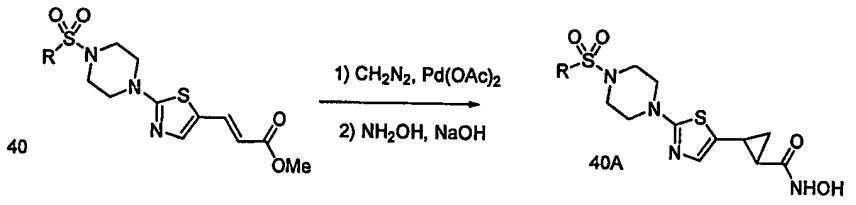
with an excess of amine in the manner described above thereby providing for compound 41.

[00132] In one alternative embodiment, commercially available 2-bromo-4-formylthiophene or 2-bromo-5-formylthiophene can be employed in the reactions recited above to provide for thiophene compounds the corresponding to thiazole compound 41.

[00133] In another alternative embodiment, the sulfonyl chloride, RSO_2Cl, can be replaced with an acid chloride, RC(O)Cl, to provide for compounds where T is carbonyl.

[00134] Still further, conventional oxidation of the sulfur in the thiophene or the thiazolyl to the corresponding sulfoxide or sulfone proceeds, for example, by contact with m-chloroperbenzoic acid.

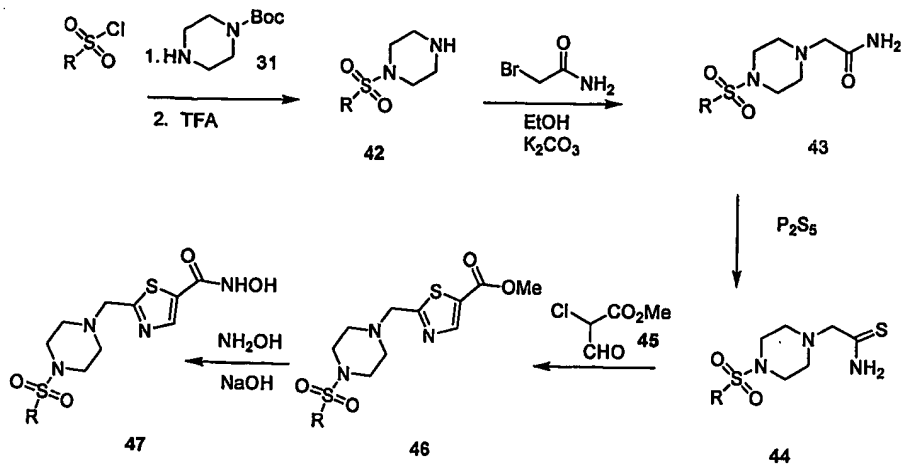
[00135] In yet another embodiment, the vinylene group of compound 40 can be converted to a cyclopropylene moiety by conventional reaction with at least an equivalent and preferably an excess of diazomethane (CH_2N_2) in the presence of a palladium diacetate as shown in Scheme 3A below:



Scheme 3A

[00136] Subsequent conversion of the carboxyl ester to the hydroxylamide proceeds as discussed above.

[00137] Scheme 4 illustrates the synthesis of compounds of formula I where Q is an alkylene group. For illustrative purposes, T is a sulfonyl group, the ring defined by A is a piperazine ring, and W is S, X is N and Y is CH.



SCHEME 4

where R and Boc are as defined above.

[00138] Specifically, an excess of sulfonyl chloride, RSO_2Cl, is combined in the manner described above with 1-t-butoxycarbonylpiperazine, compound 31, to provide 4-(RSO_2-)-1-t-butoxycarbonylpiperazine (not shown). Conventional removal of the Boc protecting group provides for 4-(RSO_2-)-piperazine, compound 42.

[00139] Coupling of compound 42 with an ω-halocarboxylamide, illustrated by 2-bromoacetamide, provides for compound 43. This conventional coupling reaction is preferably conducted in an inert solvent such as methanol, ethanol, and the like preferably in the presence of a suitable base such as potassium carbonate to scavenge the acid generated during reaction. The reaction is preferably conducted at an elevated temperature of from about 50 to about 100°C. The reaction is continued until substantial completion which typically occurs within a period of from about 2 to 48 hours. Upon completion of the reaction, compound 34 is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, evaporation and the like or, alternatively, is used in the next step without isolation and/or purification.

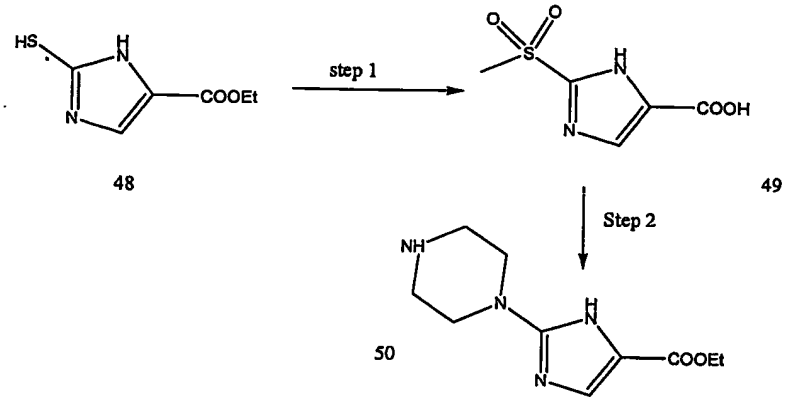
[00140] The amide of compound 43 is converted to the corresponding thioamide by conventional methods including reaction with P_2S_5 to provide for compound 44 which can be recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, evaporation and the like or, alternatively, is used in the next step without isolation and/or purification.

[00141] Compound 44 is cyclized to the corresponding thiazole derivative by reaction with methyl 2-chloro-2-formyl acetate, compound 45. In turn, this compound is prepared by reaction of methyl 2-chloroacetate and methyl formate in the presence of a suitable base. Cyclization provides for the 5-carboxylate (methyl ester) of the thiazole.

[00142] In scheme 4, the 5-carboxylate is converted to the corresponding hydroxylamide in the manner described above. It is understood, of course, that this carboxylate can be reduced to the corresponding formyl group via conventional reduction conditions well known in the art and then used in the manner of Scheme 3 to provide for the alkenylene linking group.

[00143] Compounds in Scheme 4 can be used to prepare similar compounds of formula I where T is a carbonyl group. For example, retention of the Boc protecting group throughout this reaction scheme allows for the synthesis of a Boc protected equivalent to compound 46. Removal of the Boc group followed by reaction with an acid chloride, RC(O)Cl, provides for a carbonyl equivalent of compound 46 which can then be converted to the corresponding N-hydroxylamide.

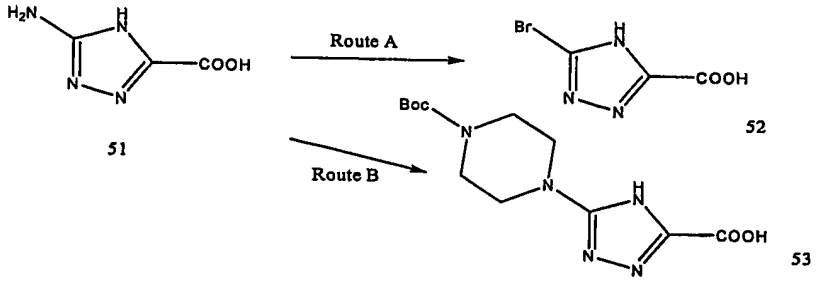
[00144] Still further, other 5 membered heteroaryl ring systems for use in this invention can be readily prepared by conventional means as shown in Schemes 4A and 4B below:



Scheme 4A

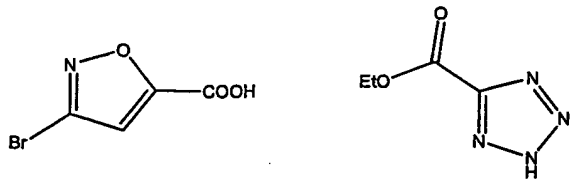
[00145] Specifically, in Scheme 4A, ethyl 2-thiol-5-carboxylimidazole compound 48, is converted to the corresponding methyl sulfone, compound 49, prepared by methylation using methyl iodide, followed by oxidation using metachloroperbenzoic acid. Subsequent re-esterification and reaction with piperazine provides for compound 50 which can be used in the procedures set forth above to provide for compounds of this invention. For example, conversion of the ethyl carboxylate to the formyl functionality proceeds via well documented reduction procedures. The formyl functionality can then be employed in a Wittig Horner reaction to provide for the vinylene carboxylate derivative in the manner described in Scheme 3 above.

[00146] Still further, Scheme 4B illustrates how commercially available 2-amino-5-carboxyl-1,3,4-triazole can be converted into intermediates which can be used in the above schemes for the synthesis of compounds of this invention.



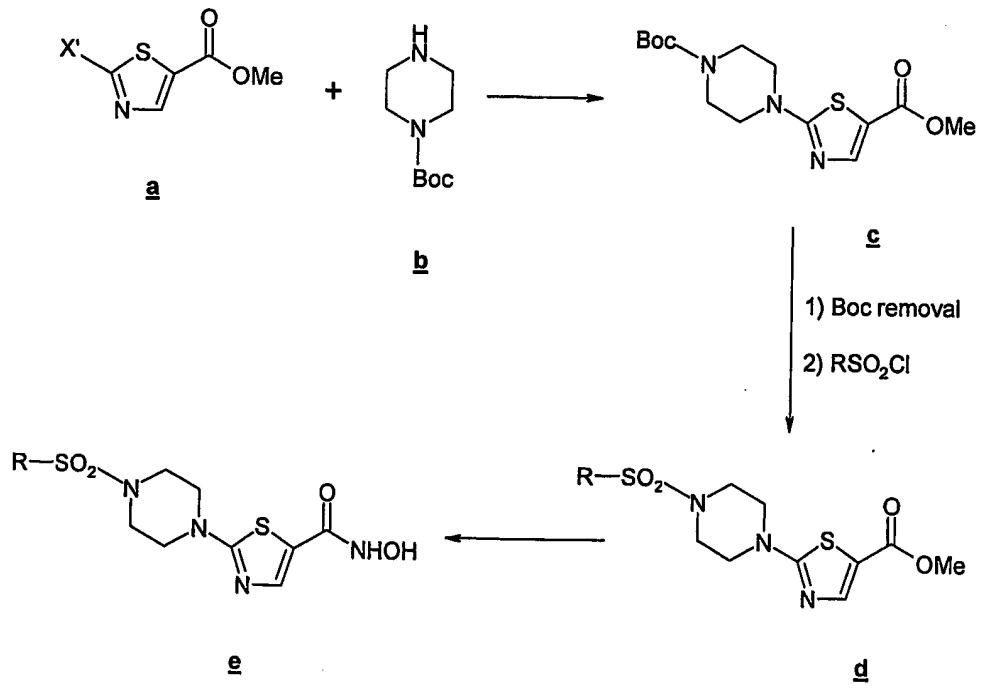
[00147] Compound 51 can be converted via conventional methods to the corresponding 2-bromo-5-carboxyl-1,3,4-triazole or the 2-(4-Boc-piperazin-1-yl)-5-carboxyl-1,3,4-triazole.

[00148] Still other heteroaryls useful in the synthetic schemes recited herein include the following commercially available compounds:



[00149] In addition to the schemes exemplified above, the compounds described, herein, particularly the compounds of formula II, and more particularly the compounds of formulas XI, XII, and XIII, may also be synthesized using the following methods.

[00150] Scheme 11 below illustrates a general method for synthesis of these compounds:



Scheme 11

[00151] where X' is a halogen such as bromo or chloro, Pg is a carboxyl protecting group such as an alkyl group (in Scheme 11, methyl) and R is as defined above.

[00152] Specifically, commercially available methyl 2-halo-5-carboxylthiazole, compound **a**, is condensed with at least an equivalent and preferably and excess of mono-protected 1-*t*-butoxycarbonyl (Boc) piperazine, compound **b**, under conventional conditions to provide for methyl 2-[(1-t-butoxycarbonyl)-piperazin-4-yl]-5-carboxylthiazole, compound **c**. The reaction is typically conducted in an inert solvent such as acetonitrile, chloroform, and the like in the presence of a suitable base such as potassium carbonate which scavenges the acid generated during the reaction. The reaction is typically conducted at an elevated temperature of from about 40° to 100°C for a period of time sufficient for substantial completion of the reaction which typically occurs within about 2 to 48 hours. The resulting product, compound **c**, can be recovered by conventional methods, such as chromatography, filtration, crystallization, evaporation and the like or, alternatively, used in the next step without purification and/or isolation.

[00153] Conventional deprotection of the Boc-protected amino group (e.g., TFA) of methyl 2-[(1-t-butoxycarbonyl)piperazin-4-yl]-5-carboxylthiazole, compound **c**, provides for the corresponding methyl 2-(piperazin-4-yl)-5-carboxylthiazole, not shown, which is then reacted with a suitable sulfonyl chloride (RSO_2Cl) to provide for the corresponding sulfonyl amide, compound **d**. This latter reaction is typically conducted by combining preferably from about 1.5 to about 2.5 equivalents, of the sulfonyl chloride in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about 0°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, N-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting methyl 2-[1-(R-sulfonylpiperazin-4-yl)]-5-carboxylthiazole,

compound **d** is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, evaporation and the like.

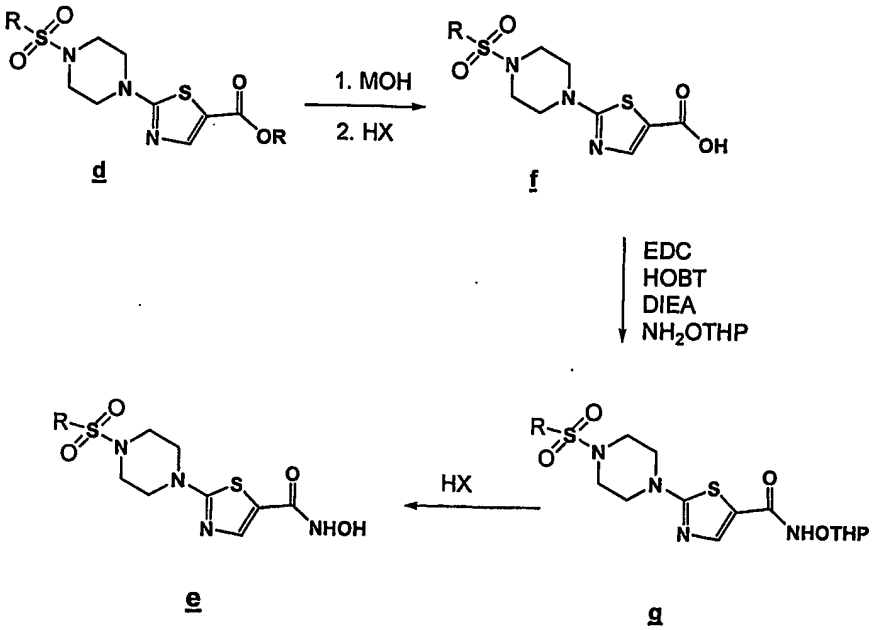
[00154] The sulfonyl chlorides employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, i.e., from compounds of the formula RSO_3H where R is as defined above, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in the range of about 0 to about 80°C for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the sulfonyl chlorides can be prepared from the corresponding thiol compound, i.e., from compounds of the formula R-SH where R is as defined herein, by treating the thiol with chlorine (Cl_2) and water under conventional reaction conditions.

[00155] Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalene-sulfonyl chloride, 2-naphthalenesulfonyl chloride, p-toluenesulfonyl chloride, 2-methylphenylsulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-tert-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethyl-benzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-

dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the N-sulfonyl amino acids.

[00156] The methyl carboxyl group of compound **d** can then be converted to a hydroxyamide by reaction with a 2-20 fold excess of hydroxylamine. The reaction is typically conducted in a suitable diluent such as a 5:2 mixture of methanol to water under basic conditions, e.g, the addition of sodium hydroxide. The reaction is typically conducted at a temperature of from about -20° to 20°C for a period of time sufficient for substantial completion of the reaction which typically occurs within about 0.5 to 10 hours. The resulting amide, compound **e**, can be recovered by conventional methods, such as chromatography, filtration, crystallization, evaporation and the like.

[00157] Alternatively, an ester **d** is converted to the hydroxamic acid **e** as shown in Scheme 12.



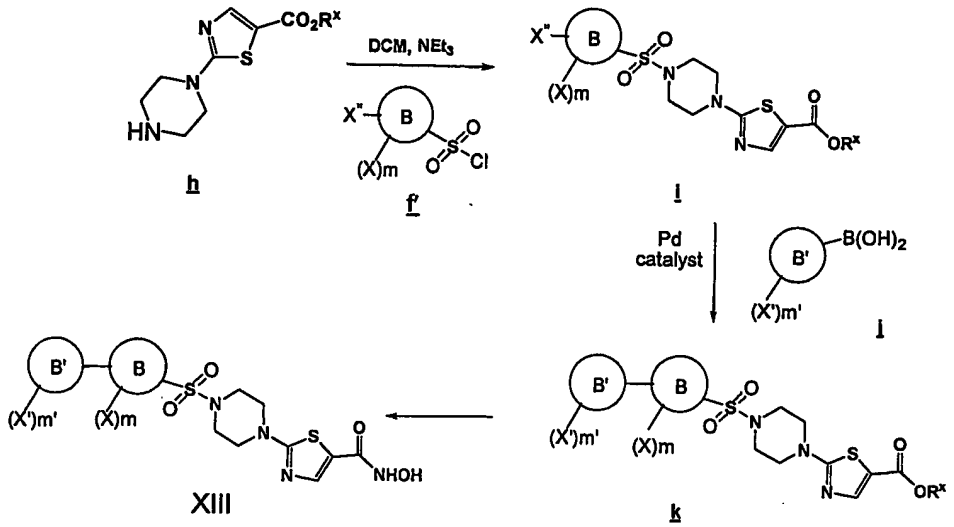
d **f** **e** **g**

Scheme 12

where X is a halo group such as chloro or bromo and M is an alkali metal such as sodium, potassium and the like.

[00158] The ester prepared by the methods of Scheme 11 is hydrolyzed to a carboxylic acid **f** with about 1-20 equivalents of an alkali metal hydroxide in a mixture of water and a suitable organic solvent in about one to 48 hours at about 20 to 100°C. Suitable organic solvents include, but are not limited to, tetrahydrofuran, ethanol, methanol, or dioxane. The reaction mixture is neutralized with an inorganic acid such as hydrochloric, hydrobromic, or sulfuric acid and the solvents are evaporated. The residue is suspended in a suitable solvent and treated with about one to five equivalents of a tertiary amine such as, but not limited to, triethylamine or diisopropylethylamine (DIEA), about one to five equivalents of *N*-hydroxybenzotriazole (HOBT), and about one to five equivalents of a carbodiimide coupling reagent such as, but not limited to, dicyclohexylcarbodiimide or 1-[3-(dimethylamino)propyl]-1-ethylcarbodiimide (EDC) and about one to five equivalents of O-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (NH_2OTHP) for about one to 48 hours at about 20 to 100 °C to produce a protected hydroxamic acid **g**. A solution of about 1 to 50% strong acid such as, but not limited to, hydrochloric acid or trifluoroacetic acid in an organic solvent such as, but not limited to, dichloromethane, dichloroethane, methanol, ethanol, or dioxane at about 0° to 80 °C in about one minute to 24 hours converts **g** to the hydroxamic acid **e** that is recovered by the means previously described.

[00159] Scheme 13, below, illustrates an alternative general synthesis of the compounds of general Formula XIII.

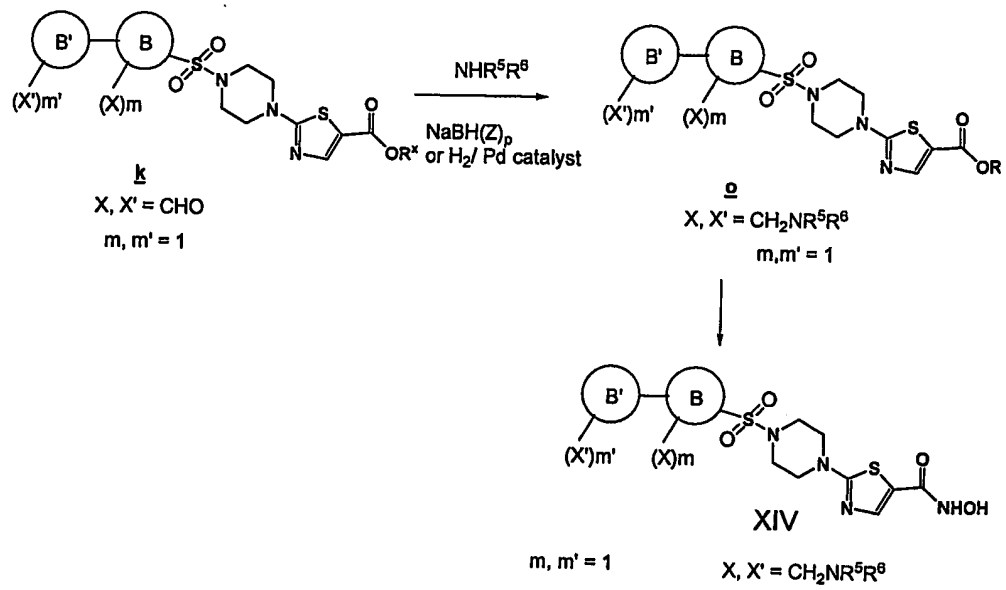


Scheme 13

where B, B′, X, X′, m, m′ are as defined, R^x is alkyl and X″ is a halo group.

[00160] The compounds of Formula XIII are synthesized wherein an aryl or heteroaryl sulfonamide **i**, prepared by the methods of Scheme 11, and bearing a halo group X″, preferably chloro, bromo, or iodo, reacts with about one to three equivalents of an aryl or heteroaryl boronic acid **j** in the presence of about one to three equivalents of a base such as an alkali metal carbonate and about 0.1 to 20 mole percent of a palladium catalyst in a suitable solvent in about one to 72 hours at about 20 to 150 °C to provide substituted biaryl, heteroaryl-aryl, aryl-heteroaryl or heteroaryl-heteroaryl sulfonamides **k**. The preferred R^x groups are methyl and ethyl. Examples of suitable solvents include, but are not limited to, dimethylformamide, dimethylacetamide, dioxane, and tetrahydrofuran. Examples of palladium catalysts include, but are not limited to, diacetoxybis(triphenylphospine)-palladium, dichlorobis(triphenylphospine)-palladium, and tetrakis(triphenylphosphine)-palladium. Examples of suitable alkali metal carbonates include, but are not limited to, sodium, potassium or cesium carbonate. Subsequent conversion of the ester **k** to the hydroxamic acids of Formula XIII are accomplished by any one of the means described in Scheme 11 or 12.

[00161] Scheme 14, below, describes the synthesis of compounds of Formula XIII wherein X or X′ is a group $-CR^3R^4NR^5R^6$ wherein R^3, R^4, R^5, and R^6 are as previously defined. Preferably, substituents R^3 and R^4 are hydrogen.



Scheme 14

[00162] A sulfonamide **k**, prepared as in Scheme 13, wherein X or X′ is an aldehyde group is reductively aminated with one to 50 equivalents of an amine, NHR^5R^6, or hydroxylamine in a suitable solvent at from about 0° to 80 °C for about one to 72 hours in the presence of about one to ten equivalents of a suitable borohydride reducing agent. Alternatively, the suitable borohydride reducing agent can be replaced by about 0.05 to 1 equivalents of a suitable palladium catalyst and about one to ten atmospheres of hydrogen. Preferred R^x groups are methyl and ethyl. Suitable solvents include, but or not limited to, methylene chloride, tetrahydrofuran, dioxane, ethanol, trimethylorthoformate, tetramethylorthoformate, ether, dichloroethane, or ethylacetate. Suitable borohydride reducing reagents include, but are not limited to, sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride. Suitable palladium catalysts include, but are not limited to, palladium on carbon, palladium on alumina, palladium on barium carbonate, or palladium

oxide. Subsequent conversion of the ester o to a hydroxamic acid is accomplished by any of the means described in Scheme 11 or 12.

Pharmaceutical Formulations

[00163] When employed as pharmaceuticals, the compounds of this invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[00164] This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula I-VII and XI-XIII. above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. The excipient employed is typically an excipient suitable for administration to human subjects or other mammals. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[00165] In preparing a formulation, it may be necessary to mill the active

[00166] compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted

by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.`

[00167] Alternatively, poorly water soluble compounds can be prepared in the form of nanoparticles to enhance their solubility. See, for example, International Patent Application Publication No. WO 03/024424 for "Stabilization of Active Agents by Formulation into Nanoparticulate Form" which is incorporated herein by reference in its entirety.

[00168] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

[00169] The compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[00170] The compounds of the present invention maybe administered to patients either alone or in combination with other known anti-tumor agents. When administered alone about 0.005 to about 100 mg/kg, more preferably about 0.005 to about 10 mg/kg, are administered to the patient Higher and lower dosages may be used. Administration may occur once a day, or several times in a day. In addition the treatment may be repeated every 7, 14, 21 or 28 days.

[00171] When administered in combination with other anti-cancer agents, the compounds of the present invention may be prepared in a formulation that includes both the compounds of Formula I-VII and one or more other anti-cancer agents. Alternatively the other anti-cancer agents may be administered in a separate formulation which may be administered before, after or simultaneously with the compounds of this invention. When administered in combination with at least one other anti-cancer agent, about 5 to about 100 mg/kg, more preferably about 0.005 to about 10 mg/kg, of the present HDAC inhibitors are administered to the patient. Higher and lower dosages may be used. The dosages of the other anti-cancer agents are known in the art. Administration may occur once a day, or several times in a day. In addition the treatment may be repeated every 7, 14, 21 or 28 days.

[00172] The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00173] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

[00174] The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[00175] The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[00176] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

[00177] The following formulation examples illustrate the pharmaceutical compositions of the present invention.

Formulation Example 1

[00178] Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

[00179] The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

[00180] A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

[00181] The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

[00182] A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Lactose	5
Active Ingredient	95

[00183] The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

[00184] Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

[00185] The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

[00186] Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

[00187] The active ingredient, cellulose, starch, an magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

[00188] Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

[00189] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

[00190] Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

[00191] The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg

Magnesium stearate	3.0 mg
Total	425.0 mg

[00192] The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Formulation Example 9

[00193] An intravenous formulation may be prepared as follows:

Ingredient	**Quantity**
Active Ingredient	250.0 mg
Isotonic saline	1000 ml

Formulation Example 10

[00194] A topical formulation may be prepared as follows:

Ingredient	**Quantity**
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

[00195] The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

[00196] Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June

11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[00197] Direct or indirect placement techniques may be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

[00198] Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Utility

[00199] Deacetylases are found in transcriptional repression pathways. In addition, histone deacetylases (HDAC) play an important role in cell proliferation and differentiation. Inhibition of histone deacetylation results in cell cycle arrest, cellular differentiation, apoptosis and reversal of the transformed phenotype. Therefore, HDAC inhibitors are useful in the treatment and/or amelioration of cell proliferative diseases or conditions, such as cancers.

[00200] Other diseases in which said HDAC inhibitors are useful are hematological disorders, e.g., hemoglobinopathies (thalassemias, sickle cell anemias); autosomal dominant disorders, e.g., spinal muscular atrophy and Huntington's disease; genetic related metabolic disorder, e.g., cystic fibrosis

and adrenoleukodystrophy (US2004/0029903 A1, US 6,124,495); psoriasis (McLaughlin, F.; La Thangue, N. B., Current Drug Targets-Inflammation, 2004, 3, 213-219); fibrosis, e.g., liver fibrosis, cirrhosis and fibrotic skin diseases, e.g., hypertrophic scars, keloid and Dupuytren's contracture (US 5,993,845); autoimmune diseases, e.g., systemic lupus erythematosus (US2003/0082666 A1); acute or chronic degenerative conditions or diseases of the eye, e.g., glaucoma, dry age-related macular degeneration, retinitis pigmentosa and other forms of heredodegenerative retinal disease, retinal detachment and tears; macular pucker, ischemia affecting the outer retina, cellular damage associated with diabetic retinopathy and retinal ischemia, damage associated with laser therapy (grid, focal, and panretinal) including photodynamic therapy, trauma, surgical (retinal translocation, subretinal surgery, or vitrectomy) or light-induced iatrogenic retinopathy, and preservation of retinal transplants (US2004/0092431 A1); ocular neovascular or edematous diseases and disorders, e.g., diabetic retinopathy, rubeosis iritis, uveitis, Fuch's heterochromatic iridocyclitis, neovascular glaucoma, corneal neovascularization, neovascularization resulting from combined vitrectomy and lensectomy, retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia, contusive ocular injury, retinopathy of prematurity, retinal vein occlusion, proliferative vitreoretinopathy, corneal angiogenesis, retinal microvasculopathy, or retinal edema (US 2004/0092558 A1); connective tissue disease, e.g., rheumatoid arthritis, progressive systemic sclerosis, sjorgren's syndrome, dermatomyositis or mixed connective tissue disease (US 2003/0206946 A1); cardiac hypertrophy and heart failure (US 6,706,686 B2); insulin resistance (US 2004/0058868 A1); amyotrophic lateral sclerosis (US 2004/0077591 A1); multiple sclerosis (US 2004/0077591 A1); Alzheimer's disease (US 2004/0077591 A1); neurodegenerative diseases (US 2004/0087657 A1); and lung diseases, e.g., cystic fibrosis, chronic obstructive pulmonary disease, asthma or acute and chronic bronchitis (US 2004/0167184 A1). Each of the above references are incorporated herein by reference in their entirety.

[00201] The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

EXAMPLES

[00202] In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

µL	=	microliter
µM	=	micromolar
µm	=	micron
Bm	=	broad multiplet
Boc	=	*N-tert*-butoxycarbonyl
Bs	=	broad singlet
Bt	=	broad triplet
Calcd	=	calculated
D	=	doublet
DCM	=	dichloromethane
Dd	=	doublet of doublets
DIEA	=	diisopropylethylamine
DMEM	=	Delbaco's minimum eagle's medium
DMF	=	N,N-dimethylformamide
DMSO	=	dimethylsulfoxide
EDC	=	1-[3-(dimethylaminopropyl]-1-ethylcarbodiimide
EtOAc	=	ethyl acetate
G	=	grams
H	=	hour
HOBt	=	N-hydroxybenzotriazole
HPLC	=	high performance liquid chromatography
HPLC %	=	Percent purity
hr or h	=	hour
L	=	liter
LCMS or LC/MS	=	liquid chromatography/mass spectrum
M	=	multiplet
M	=	molar
m/e or m/z	=	mass to charge ratio in mass spectrum
M+1	=	molecular weight + 1
Me	=	methyl
MeOH	=	methanol

Mg	=	milligram
MHz	=	megahertz
Min	=	minutes
mL	=	milliliter
Mm	=	millimeter
mM	=	millimolar
Mmol	=	millimol
N	=	normal
Nm	=	nanometers
NMR	=	nuclear magnetic resonance
Q	=	quartet
q.s.	=	means adding a quantity sufficient to achieve a certain state
RPHPLC	=	reverse phase high performance liquid chromatography
Rt	=	room temperature
Rt	=	retention time
S	=	singlet
Sec	=	seconds
T	=	triplet
TCA	=	trichloroacetic acid
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC or tlc	=	thin layer chromatography
v/v	=	volume to volume
w/v	=	weight to volume

[00203] All the chemicals starting materials were obtained from commercial suppliers and used without further purification.

[00204] Flash column chromatography was performed with silica (60-120 mesh). Analytical RPHPLC was done using Shimadzu HPLC equipped with a PDA detector using the following columns and systems: a Thermo Hypersil BDS, 4.6 x 150 mm, 5 μM particle size, C-18 column, isocratic using acetonitrile:0.1%TFA in water (60:40), flow rate = 0.5mL/min (System-1); Thermo Hypersil BDS, 4.6 x 250 mm, 5 μM particle size, C-18 column, linear gradient A-acetonitrile: B-0.1%TFA in water; 0.01min A(10%):B(90%); 5.00min A(10%):B(90%); 15.00min A(90%):B(10%); 20.00 min A(90%):B(10%); 25.00min A(10%):B(90%); 30.00min A(10%):B(90%); 30.00min Stop; flow rate = 1.5mL/min (System-2).

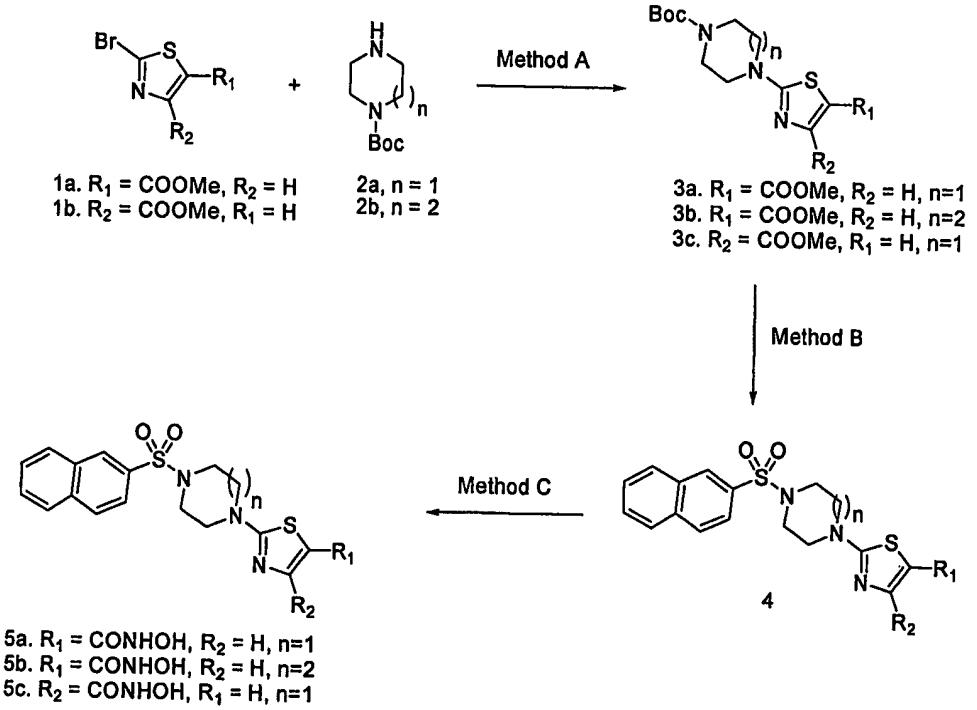
[00205] ^{1}H NMR spectra were recorded at 200 or 300 MHz and the proton chemical shifts are expressed in ppm relative to internal tetramethylsilane and coupling constants (*J*) are expressed in hertz. Mass spectra were carried out using a Micromass model.

[00206] The following examples are divided into two sections. Part I comprises examples applicable to all compounds described herein. Part II comprises examples applicable to all compounds described herein but particularly relevant to compounds of formula II, including but not limited to compounds of formula XI, XII, and XIII.

PART I

[00207] The following Scheme is referred to, below:

Scheme 5



Method A

[00208] To bromothiazole **1** (1 g, 4.18 mmol) in acetonitrile (40 ml) was added potassium carbonate (1.32 g, 10 mmol) followed by N-Boc piperizine **2a** (0.935 g, 5 mmol). The reaction mixture was held at 80°C for 16 h. At the end of the reaction time, acetonitrile was removed on roto-evaporation and the residue was taken in ethyl acetate (50 ml) and washed with brine (30 ml). The crude product **3** obtained (1.4 g, 99%) on removal of solvent was taken as such for the next reaction.

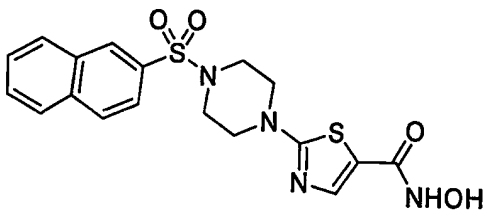
Method B

[00209] To the crude product **3** obtained from general method A (1.4 g, 4.15 mmol) TFA (20%) in dichloromethane was added and stirred at room temperature for an h. After removing the solvent, the residue was kept under high vacuum for 1 h. The residue was then redissolved in DCM (20 ml) to which triethylamine (6.0 ml, 41.5 mmol) and 2-naphthalene sulfonyl chloride (1.85 g, 8.2 mmol) was added and stirred at room temperature over night. Subsequently more DCM (50 ml) was added and washed with 1N hydrochloric acid (20 ml). The crude product obtained on removal of solvent was purified on a column chromatography using ethyl acetate in hexanes (1:1) to obtain product **4** (1.15 g, %) as white crystalline solid.

Method C

[00210] To the product **4** (200 mg, 0.46 mmol) in methanol (5 ml), aqueous hydroxyl amine (30 μL, 4.60 mmol, 50% solution) and sodium hydroxide (118 mg, 3.22 mmol, 2 ml) in water (2 ml) was added and the reaction mixture was held at 0 °C for 4 hours. After acidification with 1N HCl, the solvent was removed and the residue was taken up in ethyl acetate and washed with brine. The product **5** obtained (100 mg) on removal of solvent was purified on a RPHPLC.

Example 1



Synthesis of 1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl) piperazine

[00211] Intermediate **3a** was obtained by the general Method A using methyl 2-bromothiazole-5-caboxylate **1a** and N-Boc piperazine **2a**. TLC (Rt): 0.41 (30% EtOAc in hexanes).

[00212] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.76 (s, 1), 3.78 (s, 3), 3.66-3.69 (m, 4), 3.19-3.22 (m, 4), 1.49 (s, 9).

[00213] MS (ES +): 328 (M+1).

[00214] Intermediate **4a** was obtained by employing the general Method B using the intermediate **3a**. TLC (Rt): 0.41 (30% EtOAc in hexanes).

[00215] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32 (d, J = 1.5 Hz, 1H), 7.89-7.98 (m, 4H), 7.76 (s, 1H), 7.70-7.73 (dd, J = 1.8, 8.4 Hz, 1H), 7.61-7.66 (m, 2H), 3.78 (s, 3H), 3.66-3.69 (m, 4H), 3.19-3.22 (m, 4H).

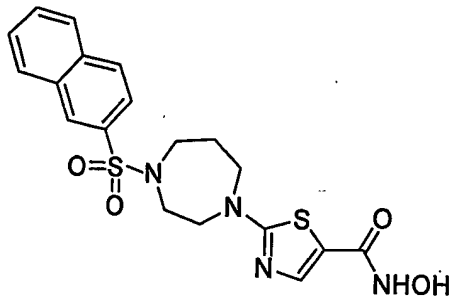
[00216] MS (ES +): 418 (M+1).

[00217] The title compound was obtained by employing the general Method C using the intermediate **4a**. TLC (Rt): 0.41 (30% EtOAc in hexanes).

[00218] ^{1}H NMR (300 MHz, CD_3OD), δ: 8.41 (m, 1H), 7.97-8.10 (m, 3H), 7.76-7.80 (dd, J = 1.8, 8.4 Hz, 1H), 7.76 (s, 1H), 7.64-7.69 (m, 2H), 3.66-3.69 (m, 4H), 3.23-3.20 (m, 4H).

[00219] MS (ES +): 419 (M+1).

Example 2



Synthesis of 1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl)-1,4-diazepane

[00220] Intermediate **3b** was obtained by the general Method A using methyl 2-bromothiazole-5-caboxylate **1a** and N-Boc homopiperazine **2b**. Yield (1.56 g, 99%). TLC (Rt): 0.33 (25% EtOAc in hexanes).

[00221] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.70 (s, 1), 3.82-3.85 (m, 2H) 3.78 (s, 3H), 3.68-3.72 (m, 2H), 3.52-3.56 (m, 2H), 3.33-3.37 (m, 2H), 2.09-2.13 (s, 2H) 1.49 (s, 9H).

[00222] MS (ES +): 342 (M+1).

[00223] Intermediate **4b** was obtained by employing the general Method B using the intermediate **3b**. Yield: 50%. TLC (Rt): 0.33 (50% EtOAc in hexanes).

[00224] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32 (m, 1H), 7.84-7.96 (m, 3H), 7.70 (s, 1H), 7.67-7.71 (m, 1H), 7.58-7.62 (m, 2H), 3.82-3.85 (m, 2H) 3.78 (s, 3H), 3.68-3.72 (m, 2H), 3.52-3.56 (m, 2H), 3.33-3.37 (m, 2H), 2.09-2.13 (s, 2H).

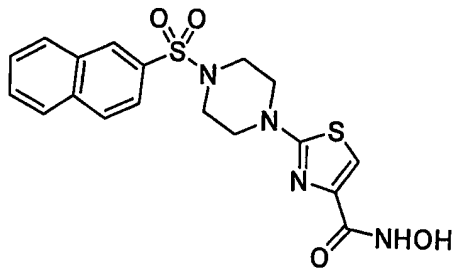
[00225] MS (ES +): 432 (M+1).

[00226] The title compound was obtained by employing the general Method C using the intermediate **4b**. TLC (Rt): 0.41 (30% EtOAc in hexanes).

[00227] ^{1}H NMR (300 MHz, CD_3OD), δ: 8.35 (m, 1H), 7.90-8.00 (m, 3H), 7.72-7.59 (dd, J = 1.8, 8.4 Hz, 1H), 7.60-7.64 (m, 2H), 7.52 (s, 1H), 3.74-3.76 (m, 2H), 3.66-3.69 (m, 4H), 3.50-3.52 (m, 2H), 1.95-2.00(m, 2H);

[00228] MS (ES +): 433 (M+1).

Example 3



Synthesis of 1-(2-naphthylsulfonyl)-4-(4-hydroxyaminocarbonylthiazol-2-yl) piperazine

[00229] Intermediate **3c** was obtained by the general Method A using methyl 2-bromothiazole-4-caboxylate **1a** and N-Boc piperazine **2a**. Yield (1.4 g, 99%). TLC (Rt): 0.37 (20% EtOAc in hexanes).

[00230] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.40 (s, 1H), 4.31 (q, J = 6.9, 13.8 Hz, 2H), 3.62-3.66 (m, 4H), 3.19-3.22 (m, 4H), 1.57 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H).

[00231] MS (ES +): 342 (M+1).

[00232] Intermediate **4a** was obtained by employing the general Method B using the intermediate **3a**. TLC (Rt): 0.41 (30% EtOAc in hexanes).

[00233] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32 (d, J = 1.5 Hz, 1H), 7.89-7.98 (m, 3H), 7.70-7.74 (dd, J = 1.8, 8.4 Hz, 1H), 7.61-7.66 (m, 2H), 7.40 (s, 1H), 4.31 (q, J = 6.9, 13.8 Hz, 2H), 3.62-3.66 (m, 4H), 3.19-3.22 (m, 4H), 1.57 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H).

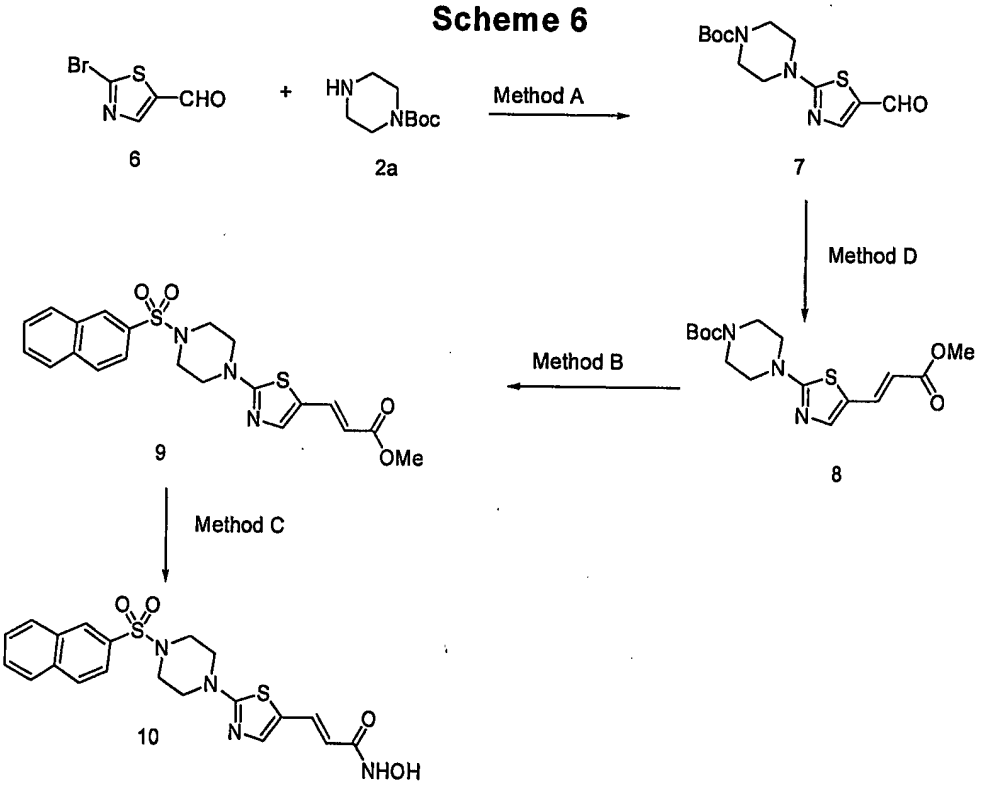
[00234] MS (ES +): 432 (M+1).

[00235] The title compound was obtained by employing the general Method C using the intermediate **4c**.

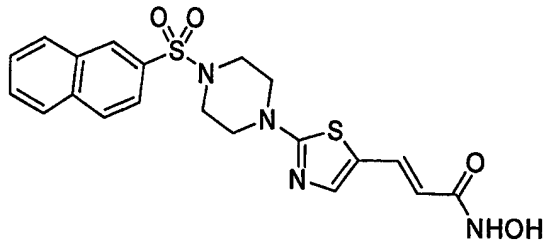
[00236] ^{1}H NMR (300 MHz, CD_3OD), δ: 8.41 (m, 1H), 7.97-8.10 (m, 3H), 7.56-7.79 (dd, J = 1.8, 8.4 Hz, 1H), 7.64-7.69 (m, 2H), 7.37 (s, 1H), 3.61-3.58 (m, 4H), 3.17-3.21 (m, 4H);

[00237] MS (ES +): 419 (M+1).

Scheme 6



Example 4



Synthesis of 1-(2-naphthylsulfonyl)-4-[(5-(2-hydroxyaminocarbonylethen-1(Z)-yl-thiazol-2yl) piperazine

[00238] Intermediate **7** was obtained by the general Method A using 2-bromo-5-formylthiazole **6** and N-Boc piperazine **2a**. Yield: 99%. TLC (Rt): 0.31 (50% EtOAc in hexanes).

[00239] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.69 (s, 1H), 7.85 (s, 1H), 3.57-3.64 (m, 8H), 1.48 (s, 9H).

[00240] MS (ES +): 298 (M+1).

[00241] Intermediate **8** was obtained by employing the Wittig Horner reaction. Accordingly, to trimethylphosphano acetate (0.23 ml, 1.60 mmol) in THF (10 ml) at – 30 °C, butyl lithium (0.64 ml, 2.5 M solution in THF) was added and stirred at -30 °C for an hour. Intermediate **7** (0.4 g, 1.35 mmol) in THF (5 ml) was then added and stirred for another 2 hours while the temperature was brought to 0 °C. After quenching the reaction with saturated aqueous ammonium chloride solution (20 ml), the product was extracted with ethyl acetate. The residue obtained on removal of solvent was purified on silica gel column chromatography using 30% ethyl acetate in hexanes (0.4 g, 84%). TLC (Rt): 0.57 (33% EtOAc in hexanes).

[00242] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.68 (d, J = 15.9 Hz, 1H), 7.34 (s, 1H), 5.80 (d, J = 15.3 Hz, 1H), 3.75 (s, 3H), 3.55 (m, 8H), 1.48 (s, 9H).

[00243] MS (ES +): 354 (M+1).

[00244] Intermediate **9** was obtained by employing the general Method B using the intermediate **8**. Yield: 0.3 g, 40%). TLC (Rt): 0.52 (50% EtOAc in hexanes).

[00245] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32 (d, J = 1.5 Hz, 1H), 7.89-7.98 (m, 3H), 7.70-7.73 (dd, J = 1.8, 8.4 Hz, 1H), 7.61-7.66 (m, 3H), 7.61 (s, 1H), 5.70 (d, J = 15.3 Hz, 1H), 3.73 (s, 3H), 3.66-3.69 (m, 4H), 3.19-3.22 (m, 4H).

[00246] MS (ES +): 444 (M+1).

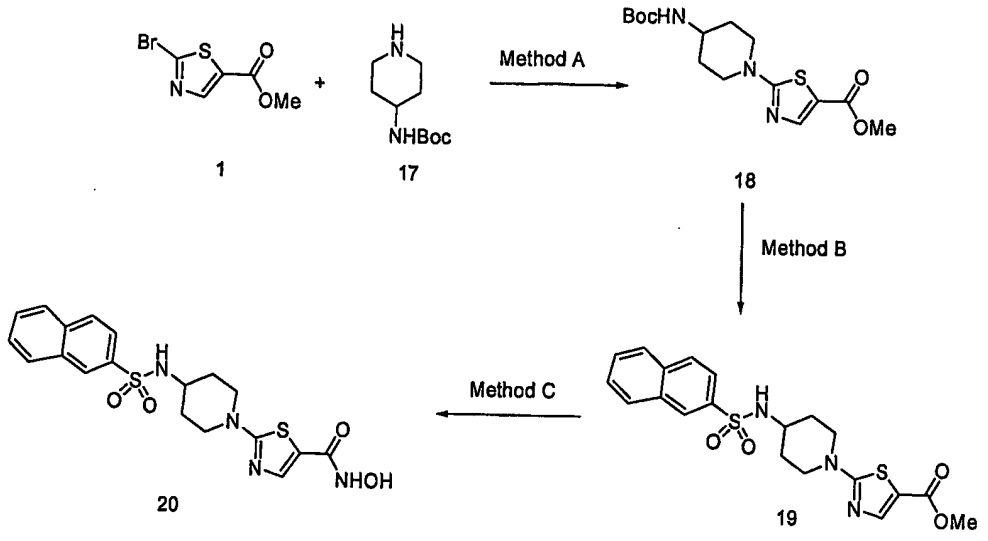
[00247] The title compound was obtained by employing the general Method C using the intermediate **9**.

[00248] ^{1}H NMR (300 MHz, DMSO-d_6), δ: 10.51 (s, 1H), 8.92 (s, 1H), 8.44 (s, 1H), 8.05-8.21 (m, 3H), 7.67-7.76 (m, 3H), 7.39 (s, 1H), 5.70 (d, J= 15.3 Hz, 1H), 3.59 (m, 4), 3.10 (m, 4H).

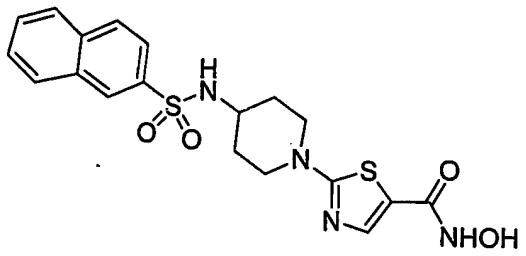
[00249] MS (ES +): 445 (M+1).

[00250] The following scheme is referred to, below:

Scheme 7



Example 5



Synthesis of 4-(2-naphthylsulfonylamino)-1-[(5-(2-hydroxyaminocarbonyl-thiazol-2-yl)-piperadine (**20**)

[00251] Intermediate **18** was obtained by the general Method A using methyl 2-bromothiazole-5-caboxylate **1** and 4-N-Boc-aminopiperidine **17**. TLC (Rt): 0.28 (25% EtOAc in hexanes).

[00252] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.79 (s, 1H), 4.63 (d, J = 7.8 Hz, 1H), 3.86-3.91 (m, 2H), 3.50 (m, 1H), 3.07-3.17 (m, 2H), 1.88-1.93 (m, 1H), 1.47-1.60 (m, 2H), 1.49 (s, 9H).

[00253] MS (ES +): 342 (M+1).

[00254] Intermediate **19** was obtained by employing the general Method B using the intermediate **18**. TLC (Rt): 0.41 (30% EtOAc in hexanes).

[00255] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.45 (d, J = 1.5 Hz, 1H), 7.89-7.98 (m, 3H), 7.80-7.84 (dd, J = 1.8, 8.4 Hz, 1H), 7.79 (s, 1H), 7.61-7.66 (m, 2H), 4.63 (d, J = 7.8 Hz, 1H), 3.86-3.91 (m, 2H), 3.50 (m, 1H), 3.07-3.17 (m, 2H), 1.88-1.93 (m, 1H), 1.47-1.60 (m, 2H), 1.49 (s, 9H).

[00256] MS (ES +): 432 (M+1).

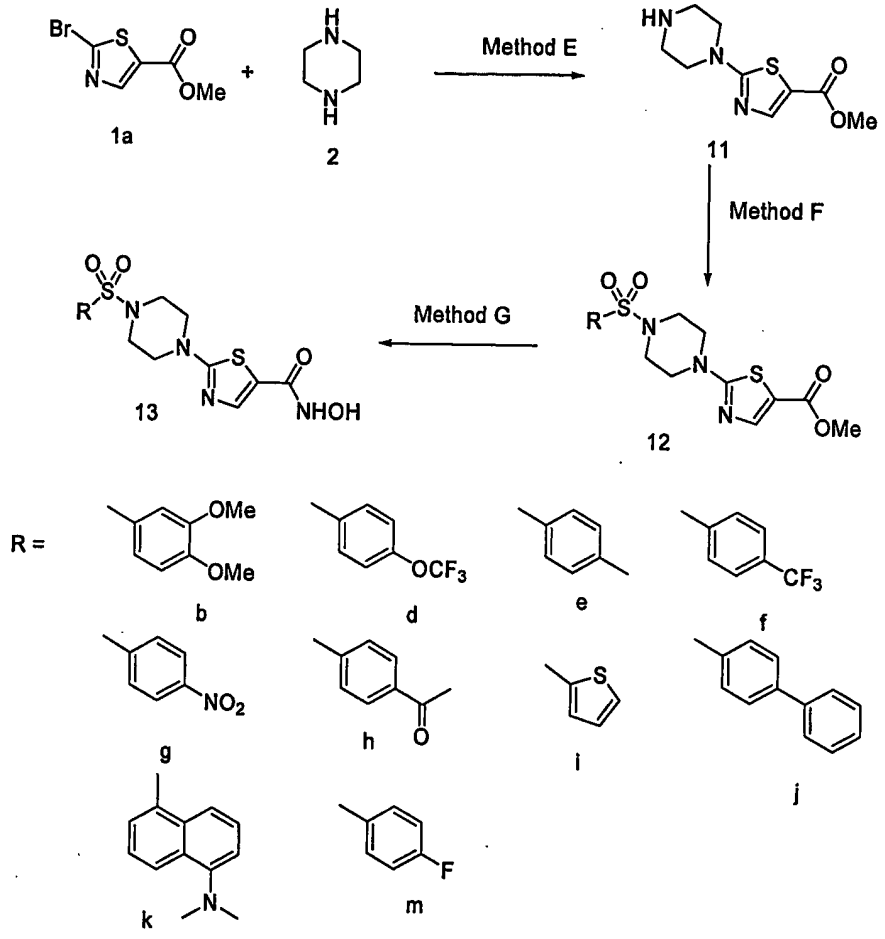
[00257] The title compound **20** was obtained by employing the general Method C using the intermediate **19**.

[00258] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.45 (d, J = 1.5 Hz, 1H), 7.96-8.07 (m, 3H), 7.85-7.89 (dd, J = 1.8, 8.4 Hz, 1H), 7.74 (s, 1H), 7.61-7.68 (m, 2H), 3.81-3.86 (m, 2H), 3.50 (m, 1H), 3.17-3.27 (m, 2H), 1.88-1.93 (m, 2H), 1.47-1.60 (m, 2H).

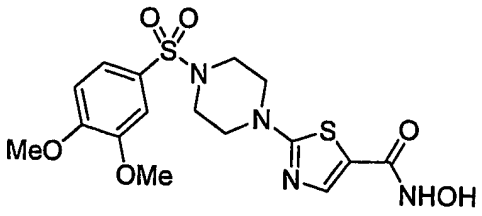
[00259] MS (ES +): 433 (M+1).

[00260] The following scheme is referred to, below:

Scheme 8



Example 6



Preparation of 2-piperazin-1-yl-thiazole-5-carboxylic acid methyl ester (11)

[00261] To a solution of methyl 2-bromothiazole-5-carboxylate (**1a**) (5.00g, 22.50 mmol) in acetonitrile (50 ml) were added piperazine **2** (2.32g, 26.97

mmol) and potassium carbonate (6.22g, 45.05 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **11** as a solid (4.10g, 79.8 %). HPLC: 92 % (Rt = 3.883 min).

[00262] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.88 (1H, s), 3.89 (3H, s), 3.55 (4H, t, *J*=6.0Hz), 2.98 (4H, t, *J* = 6.0Hz).

[00263] MS (*m/z*): 228 (M+1).

Preparation of 2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12b**)

[00264] To a solution of intermediate **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 3,4-dimethoxybenzenesulfonyl chloride (320 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12b** as a solid (200 mg, 53.0 %). HPLC: 99 % (Rt 6.507 min).

[00265] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.82 (1H, s), 7.38 (1H, dd, *J* = 2.2, 8.6Hz), 7.19 (1H, d, *J* = 2.2Hz), 6.96 (1H, d, *J* = 8.6Hz), 3.93 (6H, 2s), 3.83 (3H, s), 3.68 (4H, t, *J* = 5.2Hz), 3.14 (4H, t, *J* = 5.2Hz).

[00266] MS (*m/z*): 427 (M+1).

Preparation of 2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13b**)

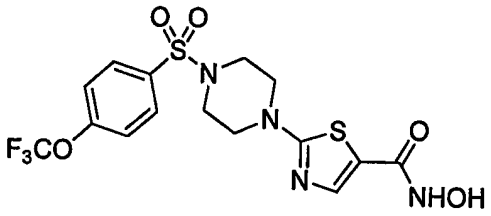
[00267] To a solution of compound (**12b**) (125 mg, 0.292 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (202 mg, 2.92 mmol)

and a freshly prepared solution of sodium methoxide in methanol (100 mg, 4.35 mmol of sodium dissolved in 1 ml of methanol) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethylacetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13b** as a solid. HPLC: 86.09% (Rt = 12.51 min).

[00268] ^{1}H NMR (CD_3OD, 200MHz): δ: 8.14 (1H, s), 7.61-7.08 (3H, m), 3.83 (6H, s), 3.54 (4H, m), 3.03 (4H, m).

[00269] MS (ES+): 429 (M+1).

Example 7



Preparation of 2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12d**)

[00270] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-trifluoromethoxybenzenesulfonyl chloride (344 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12d** as a solid (313 mg, 78.8 %). HPLC: 98 % (Rt = 12.22 min).

[00271] ^{1}H NMR ($CDCl_3$, 200MHz): δ: 7.82 (3H, m), 7.44 (2H, d, J= 8.0Hz), 3.84 (3H, s), 3.74 (4H, t, J= 5.8Hz), 3.20 (4H, t, J= 5.8Hz).

[00272] MS (*m/z*): 451 (M+1).

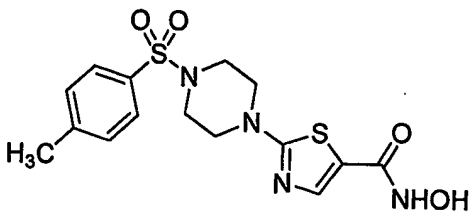
Preparation of 2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13d**)

[00273] To a solution of compound (**12d**) (125 mg, 0.276 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (191 mg, 2.76 mmol) and a freshly prepared solution of sodium methoxide in methanol (95 mg, 4.14 mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13d** as a solid (mg, %). HPLC: = 92 % (Rt = 14.16 min).

[00274] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.00 (3H, m), 7.57 (2H, m), 3.64 (4H, m), 3.19 (4H, m);

[00275] MS (*m/z*): 453 (M+1).

Example 8



Preparation of 2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (12e)

[00276] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-methyl benzenesulfonyl chloride (251 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12e** as a solid (275mg, 82%). HPLC: 99.62 % (Rt = 9.22 min).

[00277] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.82 (1H, s), 7.66 (2H, d, J = 8.4Hz), 7.35 (2H, d, J = 8.4Hz), 3.82 (3H, s), 3.68 (4H, t, J = 5.6Hz), 3.14 (4H, t, J = 5.6Hz), 2.44 (3H, s).

[00278] MS (*m/z*): 382 (M + 1).

Preparation of 2-[4-(4 toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (13e)

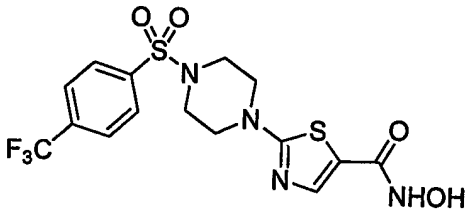
[00279] To a solution of compound **12e** (125 mg, 0.327 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (227 mg, 3.27 mmol) and a freshly prepared solution of sodium methoxide in methanol (112 mg, 4.91 mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered

off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13e** as a solid. HPLC: 90 % (Rt = 13.23 min).

[00280] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.79 (3H, m), 7.44 (2H, d, J = 8.6Hz), 3.65 (4H, t, J = 5.4Hz), 3.12 (4H, t, J = 5.4Hz), 2.46 (3H, s).

[00281] MS (*m/z*): 382.6 (M+1).

Example 9



Preparation of 2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12f**)

[00282] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-trifluromethyl benzenesulfonyl chloride (322 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12f** as a solid (333 mg, 86.9%). HPLC: 99.42 % (Rt = 11.936 min).

[00283] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.88-7.82 (5H, m), 3.81 (3H, s), 3.70 (4H, t, J = 5.2Hz), 3.19 (4H, t, J = 5.2Hz).

[00284] MS (*m/z*): 435 (M+1), 245.

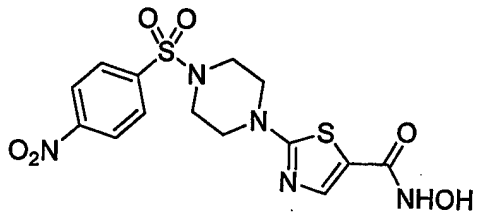
Preparation of 2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13f**)

[00285] To a solution of compound **12f** (125 mg, 0.287 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (199 mg, 2.87 mmol) and a freshly prepared solution of sodium methoxide in methanol (99 mg, 4.30 mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13f** (20 mg, yield 16%). HPLC 85.42% (Rt = 14.11 min).

[00286] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.03 (4H, m), 7.81 (1H, s), 3.75(4H, m), 3.21(4H, m).

[00287] MS (*m/z*): 436 (M+1).

Example 10



Preparation of 2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12g**)

[00288] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-nitro benzenesulfonyl chloride (292 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h.

Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12g** as a solid (120 mg, 33.3%). HPLC: 97% (Rt = 7.76 min).

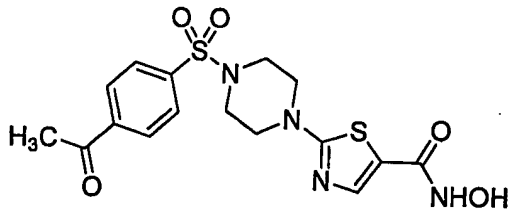
[00289] ^{1}H NMR ($CDCl_3$, DMSO-D_6, 200MHz), δ: 8.50 (2H, d, J = 8.0Hz), 8.01 (2H, d, J = 8.0Hz), 7.84 (1H, s), 3.81 (3H, s), 3.71 (4H, t, J = 5.6Hz), 3.23 (4H, t, J = 5.6Hz).

Preparation of 2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13g**)

[00290] To a solution of compound **12g** (125 mg, 0.303 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (210 mg, 3.03 mmol) and a freshly prepared solution of sodium methoxide in methanol (104 mg, 4.50 mmol of sodium dissolved in 1 ml of methanol) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13g**

[00291] MS (*m/z*): 414 (M+1).

Example 11



Preparation of 2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12h**)

[00292] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-acetyl-benzenesulfonyl chloride (288 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12h** as a solid (346mg, 96.2%). HPLC: 99.72% (Rt = 6.56 min).

[00293] ^{1}H NMR ($CDCl_3$, DMSO-D_6, 200MHz), δ: 8.10 (2H, d, J = 8.0Hz), 7.89 (2H, d, J = 8.0Hz), 7.79 (1H, s), 3.80 (3H, s), 3.69 (4H, t, J = 5.4Hz), 3.18 (4H, t, J = 5.4Hz), 2.66 (3H, s).

[00294] MS (*m/z*): 410 (M+1).

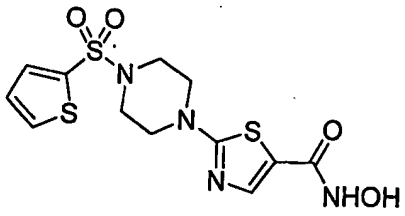
Preparation of 2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13h**)

[00295] To a solution of compound (**12h**) (125 mg, 0.305 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (211 mg, 3.05 mmol) and a freshly prepared solution of sodium methoxide in methanol (105 mg, 4.57 mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13h** (15 mg, yield 12.0 %). HPLC: 92.26% (Rt = 12.51 min).

[00296] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.86-7.68 (5H, m), 3.64 (4H, m), 3.17 (4H, m), 2.26 (3H, s).

[00297] MS (m/z): 445 (M+1).

Example 12



Preparation of 2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12i**)

[00298] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 2-thiophene sulfonyl chloride (241 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10mL) were added to the reaction mixture and the organic layer was separated, dried on sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12i** as a solid (300 mg, 91.4%). HPLC: 99.74% (Rt = 7.22 min).

[00299] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.83 (1H, s), 7.67-7.55 (2H, m), 7.16 (1H, m), 3.82 (3H, s), 3.71 (4H, t, J = 5.4Hz), 3.20 (4H, t, J = 5.4Hz).

[00300] MS (*m/z*): 373 (M+1).

Preparation of 2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13i**)

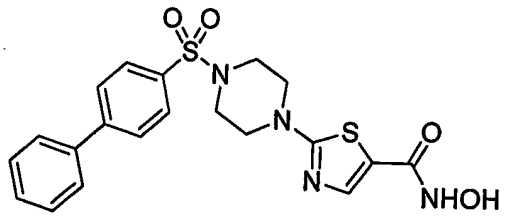
[00301] To a solution of compound **12i** (125 mg, 0.334 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (232 mg, 3.34 mmol) and a freshly prepared solution of sodium methoxide in methanol (115 mg, 5.10

mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13i** (14 mg, yield 11.2 %). HPLC: 58.9% (Rt = 12.55 min).

[00302] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.67 (1H, m), 7.85 (1H, m), 7.78 (1H, s), 7.59 (1H, m), 7.20 (1H, m), 3.67 (4H, m), 3.17 (4H, m).

[00303] MS (m/z): 375 (M+1).

Example 13



Preparation of 2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12j**)

[00304] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-biphenyl sulfonyl chloride (333 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12j** as a solid (200 mg, 51.2%). HPLC: 99.88% (Rt = 15.46 min).

[00305] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.89-7.76 (5H, m), 7.64-7.47 (5H, m), 3.82 (3H, s), 3.72 (4H, t, J = 5.1Hz), 3.22 (4H, t, J = 5.1Hz).

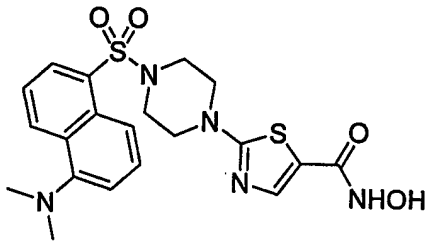
Preparation of 2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (13j)

[00306] To a solution of compound **12j** (125 mg, 0.281 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (194 mg, 2.80 mmol) and a freshly prepared solution of sodium methoxide in methanol (96 mg, 4.20mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13j** (9 mg, yield 7.2%). HPLC: 97.51% (Rt = 14.61 min).

[00307] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.91(1H, s), 7.76-7.41 (9H, m), 3.69 (4H, m), 3.21 (4H, m).

[00308] MS (m/z): 445 (M+1).

Example 14



Preparation of 2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (12k)

[00309] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 5-dimethylamino-naphthalene-1-

sulfonyl chloride (356 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12k** as a solid (233 mg, 57.50%). HPLC: 99.04 % (Rt = 12.33 min).

[00310] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 8.59 (1H, d, *J*=8.4Hz), 8.37 (1H, d, *J*= 8.4Hz), 8.21 (1H, d, *J*=7.4Hz), 7.80 (1H, s), 7.55 (2H, m), 7.19 (1H, d, *J*= 7.4Hz), 3.80 (3H, s), 3.62 (4H, t, *J*=5.6Hz), 3.32 (4H, t, *J*=5.6Hz), 2.88 (6H, s).

[00311] MS (*m/z*): 460 (M+1).

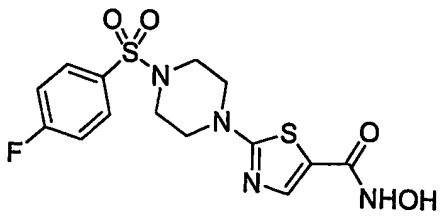
Preparation of 2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13k**)

[00312] To a solution of compound (**12k**) (125 mg, 0.270 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (187 mg, 2.70 mmol) and a freshly prepared solution of sodium methoxide in methanol (92 mg, 4.00 mmol of sodium dissolved in 1mL of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h (progress of the reaction was monitored by TLC analysis). The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13k** (10 mg, yield 8.0%). HPLC: 90.69% (Rt = 12.77 min).

[00313] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.12 (2H, m), 8.33 (1H, m), 7.86-7.59 (4H, m), 3.62 (4H, m), 3.36 (4H, m), 3.16 (6H, s).

[00314] MS (m/z): 462 (M+1).

Example 15



Preparation of 2-[4-(4-fluoro-benzene-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**12m**)

[00315] To a solution of compound **11** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 4-fluorobenzene- sulfonyl chloride (256 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **12m** as a solid (300mg, 88.4 %). HPLC: 86.16% (Rt = 7.72 min).

[00316] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.82 (1H, s), 7.78-7.75 (2H, m), 7.23 (2H, d, J = 8.8Hz), 3.81 (3H, s), 3.69 (4H, t, J = 4.8Hz), 3.14 (4H, t, J = 4.8Hz).

[00317] MS (*m/z*): 385(M+1), 101.

Preparation of 2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide (**13m**)

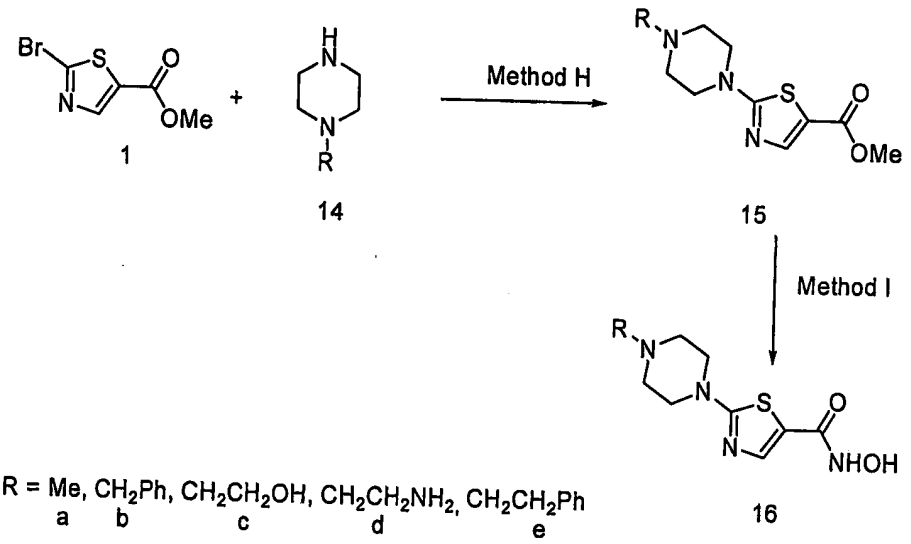
[00318] To a solution of compound (**12m**) (125 mg, 0.320 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (225 mg, 3.20 mmol) and a freshly prepared solution of sodium methoxide in methanol (110 mg, 4.80 mmol of sodium dissolved in 1 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h (progress of the reaction was monitored by TLC analysis). The reaction mixture was acidified

to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethylacetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethylacetate (5 ml) and the combined organic layers were dried on sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **13m**. HPLC: (Rt = 3.89 min).

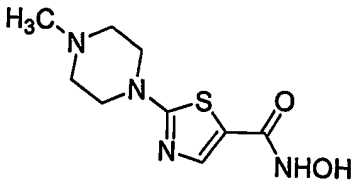
[00319] MS (m/z): 387 (M+1).

[00320] The following scheme is referred to, below:

Scheme 9



Example 16



Preparation of 2-(4-methyl-piperazin-1-yl)-thiazole-5-carboxylic acid methyl ester (**15a**)

[00321] To a solution of methyl 2-bromothiazole-5-carboxylate **1** (222 mg, 1.00 mmol) in acetonitrile (20 ml) were added N-methyl piperazine **14a** (120

mg, 1.20 mmol) and potassium carbonate (152 mg, 1.10 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **16a** (188 mg, 78.1 %).

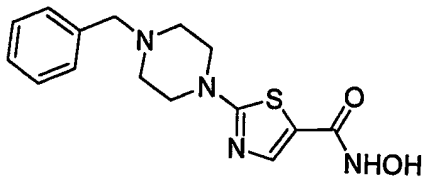
[00322] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.93 (1H, s), 3.83 (3H, s); 3.67 (4H, m), 2.75 (4H, t, J = 5.0Hz), 2.49 (3H, s).

[00323] MS (*m/z*): 242 (M+1).

Preparation of 2-(4-methyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide (**16a**)

[00324] To a solution of compound **15a** (125 mg, 0.518 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (360 mg, 5.18 mmol) and a freshly prepared solution of sodium methoxide in methanol (178 mg, 7.72 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **16a.** HPLC: (Rt = 10.74 min).

Example 17



Preparation of 2-(4- Benzyl -piperazin-1-yl)-thiazole-5-carboxylic acid methyl ester (15b)

[00325] To a solution of methyl 2-bromothiazole-5-carboxylate **1** (222 mg, 1.00 mmol) in acetonitrile (20 ml) were added N-benzyl piperazine **14b** (211 mg, 1.20 mmol) and potassium carbonate (152 mg, 1.10 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **15b** (229 mg, 72.7%).

[00326] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.87 (1H, s), 7.40 (5H, m), 3.84 (3H, s), 3.61 (6H, m), 2.60 (4H, t, J = 5.0Hz).

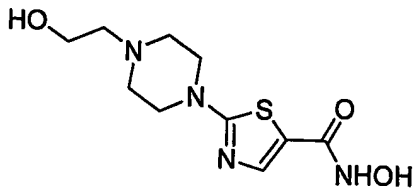
[00327] MS (*m/z*): 318 (M+1).

Preparation of 2-(4-Benzyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide (16b-hydroxamate)

[00328] To a solution of compound **15b** (125 mg, 0.394 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (273 mg, 3.94 mmol) and a freshly prepared solution of sodium methoxide in methanol (136 mg, 5.911 mmol of sodium dissolved in 1.5 ml of methanol) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered

and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **16b**. HPLC: (Rt = 4.45 min).

Example 18



Preparation of 2-[4-(2-hydroxyethyl) -piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**15c**)

[00329] To a solution of methyl 2-bromothiazole-5-carboxylate 1 (222 mg, 1.00 mmol) in acetonitrile (20 ml) were added N-(2-hydroxyethyl) piperazine **14c** (156 mg, 1.20 mmol) and potassium carbonate (152 mg, 1.10 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **15c** (185mg, 68.2%).

[00330] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.81 (1H, s), 3.79 (3H, s), 3.70 (2H, t, J=5.4Hz), 3.63 (4H, t, J = 5.6Hz), 2.70 (6H, m).

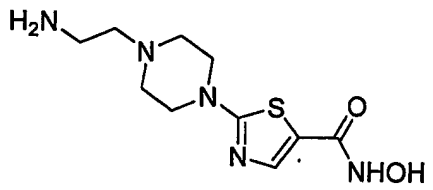
[00331] MS (*m/z*): 272 (M+1).

Preparation of 2-(4-(2-hydroxyethyl) -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide (**16c**)

[00332] To a solution of compound **15c** (125 mg, 0.461 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (320 mg, 4.61 mmol) and a freshly prepared solution of sodium methoxide in methanol (159 mg, 6.91 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered

and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **16c**. HPLC: (Rt = 2.97 min).

Example 19



Preparation of 2-[4-(2-aminoethyl) -piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**15d**)

[00333] To a solution of methyl 2-bromothiazole-5-carboxylate **1** (222 mg, 1.00 mmol) in acetonitrile (20 ml) were added N-(2-amino ethyl) piperazine **14d** (155 mg, 1.20 mmol) and potassium carbonate (152 mg, 1.10 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **15d** (176 mg, 65.2%).

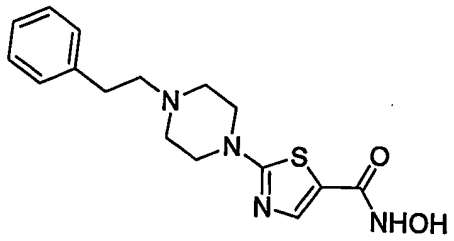
[00334] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.82 (1H, s), 7.23 (5H, m), 3.81 (3H, s), 3.60 (4H, t, J = 5.0Hz), 2.90-2.63 (8H, m).

Preparation of 2-(4-(2-aminoethyl) -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide (**16d**)

[00335] To a solution of compound **15d** (125 mg, 0.462 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (321 mg, 4.62 mmol) and a freshly prepared solution of sodium methoxide in methanol (159 mg, 6.91 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethylacetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethylacetate (5 ml) and the combined organic layers were dried on sodium sulphate, filtered

and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **16d.** HPLC: (Rt = 2.93 min).

Example 20



Preparation of 2-[4-phenylethyl-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**15e**)

[00336] To a solution of methyl 2-bromothiazole-5-carboxylate **1** (222 mg, 1.00 mmol) in acetonitrile (20 ml) were added N-phenyl ethyl piperazine **14e** (228 mg, 1.20 mmol) and potassium carbonate (152 mg, 1.10 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **15e** (245 mg, 66.4%).

[00337] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.78 (1H, s), 3.81 (3H, s), 3.62 (4H, m), 2.77-2.31 (8H, m).

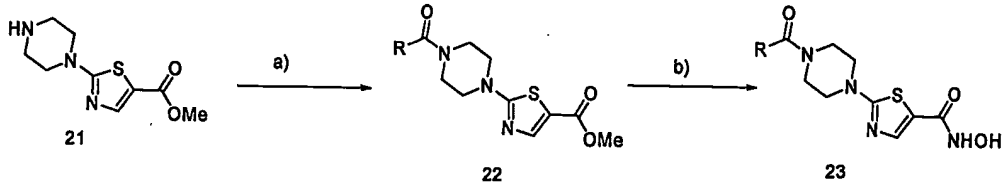
Preparation of 2-(4-phenylethyl -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide (**16e**)

[00338] To a solution of compound **15e** (125 mg, 0.377 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (262 mg, 3.77 mmol) and a freshly prepared solution of sodium methoxide in methanol (130 mg, 5.655 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate

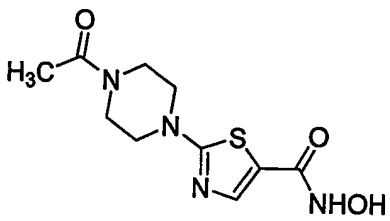
(5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **16e**. HPLC: (Rt = 13.41 min).

[00339] The following scheme is referred to, below:

Scheme 10



Example 21



Preparation of 2-(4-acetyl-piperazin-1-yl)-thiazole-5-carboxylic acid methyl ester (**22a**)

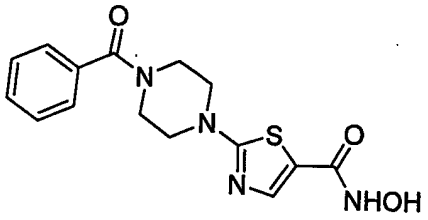
[00340] To a solution of compound **21** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added acetic anhydride (107 mg, 1.056 mmol) and triethylamine (106 mg, 1.056 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h (progress of the reaction was monitored by TLC analysis). Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **22a** (120 mg, yield 50.8%). HPLC: Rt = 4.14.

[00341] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.82 (1H, s), 3.84 (3H, s), 3.77 (4H, t, J=5.4Hz), 3.54 (4H, t, J = 5.4Hz), 2.15 (3H, s).

Preparation of 2-(4-acetyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide (**23a**)

[00342] To a solution of compound **22a** (100 mg, 0.300 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (208 mg, 2.991 mmol) and a freshly prepared solution of sodium methoxide in methanol (103 mg, 4.511 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **23a**. HPLC: Rt = 4.42 min.

Example 22



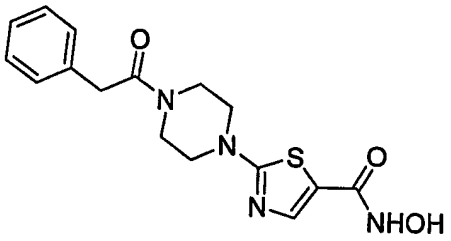
Preparation of 2-(4-benzoyl-piperazin-1-yl)-thiazole-5-carboxylic acid methyl ester (**22b**)

[00343] To a solution of compound **21** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added benzoyl chloride (148 mg, 1.056 mmol) and triethylamine (106 mg, 1.047 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h (progress of the reaction was monitored by TLC analysis). Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **22b** (180 mg, yield 61.8%).

Preparation of 2-(4-benzoyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide (**23b**)

[00344] To a solution of compound **22b** (100 mg, 0.321 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (222 mg, 3.191 mmol) and a freshly prepared solution of sodium methoxide in methanol (110 mg, 4.712 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **23b.** HPLC: Rt = 3.69 min.

Example 23



Preparation of 2-(4-phenylacetyl-piperazin-1-yl)-thiazole-5-carboxylic acid methyl ester (**22c**)

[00345] To a solution of compound **21** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added phenyl acetyl chloride (162 mg, 1.056 mmol) and triethylamine (106 mg, 1.047 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h (progress of the reaction was monitored by TLC analysis). Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **22c** (130 mg, yield 42.9%). HPLC: 99.40 0% (Rt = 11.93 min).

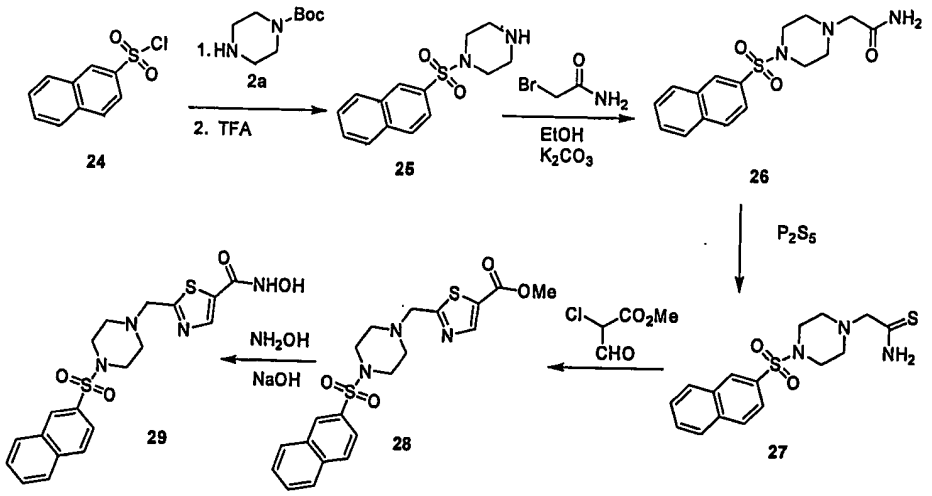
[00346] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.85 (1H, s), 7.27(5H, m), 3.82 (3H, s), 3.73 (4H, m), 3.51 (4H, m), 3.34 (2H, m).

Preparation of 2-(4-phenylacetyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide (**23c**)

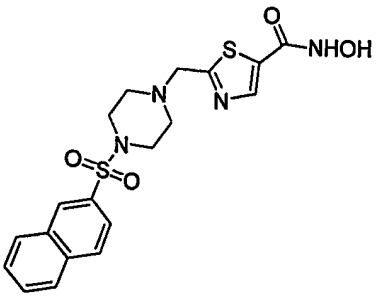
[00347] To a solution of compound **22c** (100 mg, 0.377 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (208 mg, 3.771 mmol) and a freshly prepared solution of sodium methoxide in methanol (103 mg, 4.471 mmol of sodium dissolved in 1.5 ml of methanol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 2h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethyl acetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **23c**. HPLC: Rt = 5.62 min.

[00348] The following scheme is referred to, below:

Scheme 11



Example 24



Preparation of N-(2-napthylsulfonyl)piperazine (25)

[00349] A solution of N-tert-butyoxycarbonylpiperazine (2a) (1.86 g) in DCM (100 ml) and N,N-di-2-propyl-ethylamine (2 ml) was cooled in ice-water as a solution of 2-naphthalenesulfonylchloride (2.27 g) in DCM (50 ml) was added drop-wise. After addition, the cooling was removed and the reaction stirred overnight. The solvent was evaporated and the residue partitioned between water and ethyl acetate. The organic phase was sequentially washed with 0.5 N hydrochloric acid, water, saturated aqueous sodium bicarbonate and brine. After drying, the solvent was evaporated to provide a white solid. The white solid was dissolved in DCM (35 ml) and treated with trifluoroacetic acid (15 ml). After one hour, the solvent was evaporated, the residue suspended in water and the solution made basic with 1 N sodium hydroxide. The mixture was extracted with ethyl acetate. The extracts were washed with water, dried, and the solvent evaporated to give a white solid (2.7 g).

[00350] ^{1}H NMR (CD_3OD, 300 MHz), δ: 8.41 (s, 1H), 8-8.13 (3H, m), 7.6-7.8 (3H, m), 3.17-3.21 (4H, m), 3.09-3.13 (4H, m).

Preparation of N-(2-naphthylsulfonyl)-N'-(2-acetamido)piperazine (26)

[00351] A mixture of **25** (2.2 g), 2-bromoacetamide (1.15 g) potassium carbonate (1.16 g) and ethanol (40 ml) was heated to reflux overnight. The solvent was evaporated and the residue suspended in water and stirred for 30 minutes. The solid was collected by filtration and thoroughly dried to give a white solid (2.8 g).

[00352] ^{1}H NMR (CD_3OD, 300 MHz), δ: 8.39 (s, 1H), 7.99-8.11 (m, 3H), 7.63-7.79 (m, 3H), 3.14 (m, 4H), 2.98 (s, 2H), 2.60 (t, 4H).

Preparation of N-(2-naphthylsulfonyl)-N'-(2-thioacetamido)piperazine (27)

[00353] A suspension of **26** (0.94 g) in tetrahydrofuran (10 ml) was stirred as phosphorus pentasulfide (1.89 g) was added in portions. The reaction was then heated to reflux for one hour. The solvent was decanted and the solid residue triturated with tetrahydrofuran. The solvent was evaporated from the extracts and the residue purified by flash chromatography on 30 g of silica gel eluting with 1:1 ethyl acetate:hexane. The desired component was finally eluted with 60% ethyl acetate-hexane. Evaporation of the pure fractions gave a white solid (0.23 g).

[00354] ^{1}H NMR (CD_3OD, 300 MHz), δ: 8.27 (s, 1H), 7.88-8.0 (m, 3H), 7.52-7.68 (m, 3H), 3.23 (s, 2H), 3.03 (m, 4H), 2.46 (t, 4H).

[00355] MS (EI+): 350 (m + 1).

Preparation of methyl chloro(formyl)acetate

[00356] Methyl chloroacetate (3.2 g) and methyl formate (1.8 g) were dissolved in toluene (5 ml) and the mixture was cooled in ice-water. Sodium methoxide (2 g) was added in portions and the reaction stirred for five hours. The reaction was quenched with water (100 ml) and the mixture was extracted with toluene (100 ml) and ether (100 ml). The aqueous layer was separated, cooled in ice-water, and the pH of the solution adjusted to 4 using 6 N hydrochloric acid. The aqueous layer was then extracted with ethyl acetate. The organic extracts were dried and the solvent thoroughly evaporated to give a tacky solid (2 g) that was used without further purification. TLC on silica gel eluting with 1:1 ethyl acetate:hexane shows two spots R_f = 0.36 and 0.38.

Preparation of N-(2-naphthylsulfonyl)-N'-[2-(5-carbomethoxy) thiazolyl] piperazine (**28**).

[00357] A mixture of **27** (84 mg) and methyl chloro(formyl)acetate (180 mg) in toluene (3 ml) was heated to reflux for three hours. The reaction was diluted with ethyl acetate and washed sequentially with aqueous, saturated sodium bicarbonate, 10% aqueous potassium carbonate and water. The organic layer was dried and the solvent evaporated to give a brown, oily residue. The residue was purified by flash chromatography on silica gel (15 g) eluting with 1:1 ethyl acetate:hexane. The desired fractions were eluted with 60% ethyl acetate-hexane. Evaporation of the purest fraction gave a brown glass (40 mg).

[00358] ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.33 (s, 1H), 8.23 (s, 1H), 7.92-8.0 (m, 3H), 7.6-7.76 (m, 3H), 3.836 (s, 3H), 3.828 (s, 2H), 3.15 (m, 4H), 2.71 (m, 4H).

[00359] MS (EI+): 432 (m + 1).

Preparation of N-(2-naphthylsulfonyl)-N'-{2-[5-(N-hydroxycarboxamido)] thiazolyl}-piperazine (**29**).

[00360] A solution of **28** (32 mg) in ethanol (1.5 ml) was cooled in ice-water. A solution of 50% aqueous hydroxyl amine (50 μL) was added followed by 1 N sodium hydroxide (53 μL). After four hours, the cooling was stopped and the reaction stirred overnight. Additional 50% hydroxyl amine (25 μL) and 1 N sodium hydroxide (20 μL) were added and stirring continued for eight hours. The reaction was neutralized with 1 N hydrochloric acid (70 μL) and the solvent was evaporated to give a yellowish solid. This product was purified by HPLC using a 19 x 50 mm C-18 column eluting with a ten minute linear gradient that started with 100% water-0.1% trifluoroacetic acid and ended with 30% water-0.1% trifluoroacetic acid/70% acetonitrile-0.1% trifluoroacetic acid. The pure fractions of the component eluting at 4.8 minutes were freeze dried to give a white solid (0.1 mg).

[00361] MS (EI+): 433 (m + 1).

Biological Examples

Example A

In vitro fluorescent histone deacetylase assay

[00362] Histone deacetylase (HDAC) activity assays were performed using the HDAC fluorescent activity assay/drug discovery kit (Biomol Research Laboratories, Plymouth Meeting, PA) essentially according to the manufacturer's instructions. The included HeLa cell nuclear extract, which contains a mosaic of HDAC enzymes and other nuclear factors, was used as the source of HDAC activity. The final substrate concentration in the assay mixture was 50 μM. The reaction was allowed to proceed for 10 min at room temperature before stopping the reaction. Test compounds were prepared as 20 mM stock solutions in DMSO (Molecular Biology grade, Sigma-Aldrich Co., St. Louis, MO) and stored at -70 °C. Serial dilutions of test compounds were prepared in assay buffer immediately prior to testing. DMSO was determined in a separate trial to have no significant effect on the activity of this assay at concentrations up to 5%; the final DMSO concentration in the wells was no more than 2% and therefore DMSO effects were safely neglected. Assays were performed in white polystyrene 96-well half-area assay plates (Corning, Corning, NY) and measured on a Wallace 1420 fluorescent plate reader (Wallac Oy, Turku, Finland) with an excitation wavelength of 355 nm, an emission wavelength of 460 nm, and a 1 sec signal averaging time.

[00363] In some assays recombinant HDAC8 (Biomol) was used as the source of the enzyme activity; here the final substrate concentration was 250 μM, the final concentration of HDAC8 was 0.02 u/μL and the reaction was allowed to proceed at 37 °C for 1 h before stopping. For all curves, IC_{50} values were calculated with the GraFit curve-fitting program (Erithacus, Horley, Surrey, UK).

Example B

Whole Cell Cytotoxicity Assay:Sulforhodamine B

[00364] The following procedure can be found on the Developmental Therapeutics Program NCI/NIH web site at http://dtp.nci.nih.gov/brancehes/btb/ivclsp.html.

[00365] 1. Human tumor cell lines of HT29, A549 and MCF7 are grown in DMEM containing 10% fetal bovine serum and 2mM L-glutamine. Cells are plated in a 96 well plate at a density of 5000 cells per well in 100 uL of growth medium and incubated at 37°C, 5% CO_2, for 24 hours prior to the addition of experimental compounds.

[00366] 2. Experimental drugs are solubilized in DMSO for a final concentration of 20mM immediately prior to use. Drugs are further diluted in growth media for a total of nine drug concentrations and a growth control. At the 24 hour time point, one plate of cells is fixed in situ with TCA as a measurement of the cell population at time zero, or the time of drug addition.

[00367] 3. The plates are further incubated with drug for an additional 48 hours.

[00368] 4. The cells are fixed in situ by gently aspirating off the culture media and then adding 50 uL of ice cold 10% TCA per well and incubated at 4°C for 60 minutes. The plates are washed with tap water five times and allowed to air dry for 5 minute.

[00369] 5. 50ul of a 0.4% (w/v) Sulforhodamine B solution in 1% (v/v) acetic acid is added per well and incubated for 30 minutes at room temperature.

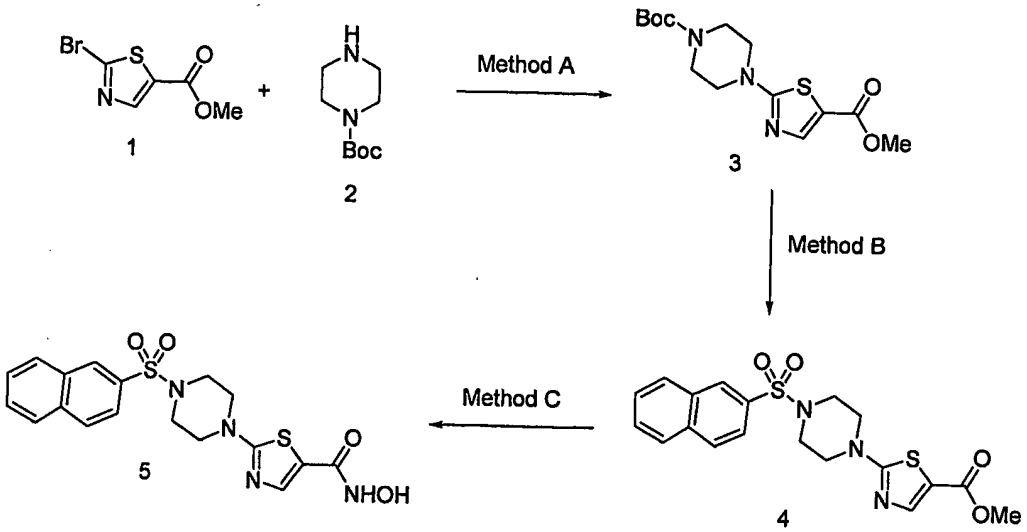
[00370] 6. Following staining, plates are washed five times with 1% acetic acid to remove any unbound dye and then allowed to air dry for 5 minutes.

[00371] 7. Stain is solubilized with 100 uL of 10 mM Tris pH 10.5 per well and placed on an orbital rotator for 5 minutes.

[00372] 8. Absorbance is read at 570 nm.

PART II

[00373] The following Scheme is referred to, below:



Scheme 15

Example 201

Synthesis of 2-[4-(naphtha-2-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[Alternative Nomenclature -- 1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl) piperazine]

Method A

[00374] To bromothiazole **1** (1 g, 4.18 mmol) in acetonitrile (40 ml) was added potassium carbonate (1.32 g, 10 mmol) followed by N-Boc piperizine **2** (0.935 g, 5 mmol). The reaction mixture was held at 80°C for 16 h. At the end of the reaction time, acetonitrile was removed on roto-evaporation and the residue was taken in ethyl acetate (50 ml) and washed with brine (30 ml). The

crude product **3** obtained (1.4 g, 99%) on removal of solvent was taken as such for the next reaction.

[00375] TLC (Rf): 0.41 (30% EtOAc in hexanes).

[00376] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.76 (s, 1), 3.78 (s, 3), 3.66-3.69 (m, 4), 3.19-3.22 (m, 4), 1.49 (s, 9). MS (ES +): 328 (M+1).

Method B

[00377] To the crude product **3** obtained from method A (1.4 g, 4.15 mmol) TFA (20%) in dichloromethane was added and stirred at room temperature for an h. After removing the solvent, the residue was kept under high vacuum for 1 h. The residue was then redissolved in DCM (20 ml) to which triethylamine (6.0 ml, 41.5 mmol) and 2-naphthalene sulfonyl chloride (1.85 g, 8.2 mmol) was added and stirred at room temperature over night. Subsequently more DCM (50 ml) was added and washed with 1N hydrochloric acid (20 ml). The crude product obtained on removal of solvent was purified on a column chromatography using ethyl acetate in hexanes (1:1) to obtain product **4** (1.15 g, %) as white crystalline solid.

[00378] TLC (Rf): 0.41 (30% EtOAc in hexanes).

[00379] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32 (d, J = 1.5 Hz, 1H), 7.89-7.98 (m, 4H), 7.76 (s, 1H), 7.70-7.73 (dd, J = 1.8, 8.4 Hz, 1H), 7.61-7.66 (m, 2H), 3.78 (s, 3H), 3.66-3.69 (m, 4H), 3.19-3.22 (m, 4H). MS (ES +): 418 (M+1).

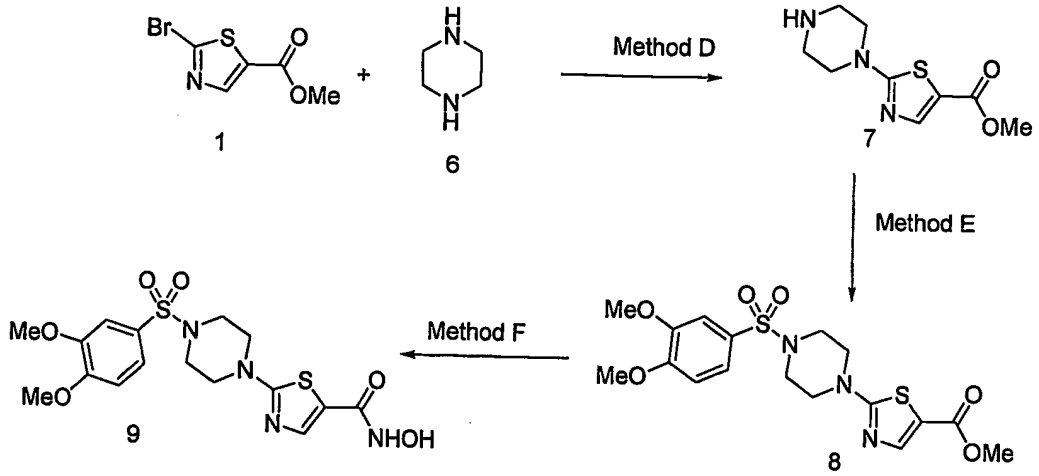
Method C

[00380] To the product **4** (200 mg, 0.46 mmol) in methanol (5 ml), aqueous hydroxyl amine (30 µL, 4.60 mmol, 50% solution) and sodium hydroxide (118 mg, 3.22 mmol, 2 ml) in water (2 ml) was added and the reaction mixture was held at 0 °C for 4 hours. After acidification with 1N HCl, the solvent was removed and the residue was taken up in ethyl acetate and washed with brine. The product **5** obtained (100 mg) on removal of solvent was purified on a RPHPLC.

[00381] TLC (Rf): 0.41 (30% EtOAc in hexanes).

[00382] ^{1}H NMR (300 MHz, CD_3OD), δ: 8.41 (m, 1H), 7.97-8.10 (m, 3H), 7.76-7.80 (dd, J = 1.8, 8.4 Hz, 1H), 7.76 (s, 1H), 7.64-7.69 (m, 2H), 3.66-3.69 (m, 4H), 3.23-3.20 (m, 4H). MS *m/e*: 418 (M+1).

[00383] The following scheme is referred to, below:



Scheme 16

Example 202

Preparation of 2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

Method D

[00384] To a solution of methyl 2-bromothiazole-5-carboxylate **1** (5.00 g, 22.50 mmol) in acetonitrile (50 ml) were added piperazine **6** (2.32 g, 26.97 mmol) and potassium carbonate (6.22 g, 45.05 mmol) under a N_2 atmosphere. The reaction mixture was heated to reflux at 80°C for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give 2-piperazin-1-yl-thiazole-5-carboxylic acid methyl ester **7** as a solid (4.10g, 79.8 %).

[00385] HPLC: 92 % (Rt = 3.883 min).

[00386] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.88 (1H, s), 3.89 (3H, s), 3.55 (4H, t, *J*=6.0Hz), 2.98 (4H, t, *J* = 6.0Hz). MS (*m/z*): 228 (M+1).

Method E

[00387] To a solution of intermediate **7** (200 mg, 0.886 mmol) in dichloromethane (7.5 ml) were added 3,4-dimethoxybenzenesulfonyl chloride (320 mg, 1.320 mmol) and triethylamine (220 mg, 2.169 mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound 2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid methyl ester (**8**) as a solid (200 mg, 53.0 %).

[00388] HPLC: 99 % (Rt 6.507 min).

[00389] ^{1}H NMR ($CDCl_3$, 200MHz), δ: 7.82 (1H, s), 7.38 (1H, dd, *J* = 2.2, 8.6Hz), 7.19 (1H, d, *J* = 2.2Hz), 6.96 (1H, d, *J* = 8.6Hz), 3.93 (6H, 2s), 3.83 (3H, s), 3.68 (4H, t, *J* = 5.2Hz), 3.14 (4H, t, *J* = 5.2Hz).

[00390] MS (*m/z*): 427 (M+1).

Method F

[00391] To a solution of compound **8** (125 mg, 0.292 mmol) in 1,4-dioxane (2 ml) were added hydroxylamine hydrochloride (202 mg, 2.92 mmol) and a freshly prepared solution of sodium methoxide in methanol (100 mg, 4.35 mmol of sodium dissolved in 1 ml of methanol) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH ~ 6 with 1M HCl and the formed precipitates were filtered off. The filtrate was diluted with ethylacetate (5 ml) and water (2 ml) and the organic layer was separated. The aqueous layer was washed with ethyl acetate

(5 ml) and the combined organic layers were dried on sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to give **9** as a solid.

[00392] HPLC: 86.09% (Rt = 12.51 min).

[00393] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.14 (1H, s), 7.61-7.08 (3H, m), 3.83 (6H, s), 3.54 (4H, m), 3.03 (4H, m).

[00394] MS *m/e*: 429 (M+1).

[00395] Following the procedures set forth in Example 202 above, the compounds of following examples were prepared using the appropriate starting materials and the ^{1}H NMR data, HPLC and/or mass spectral data are presented below.

Example 203

2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00396] Same as Example 7.

Example 204

2-[4-(4-toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00397] Same as Example 8.

Example 205

2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00398] Same as Example 9.

Example 206

2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00399] Same as Example 10.

Example 207

2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00400] Same as Example 11.

Example 208

Preparation of 2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00401] Same as Example 12.

Example 209

2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00402] Same as Example 13.

Example 210

2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

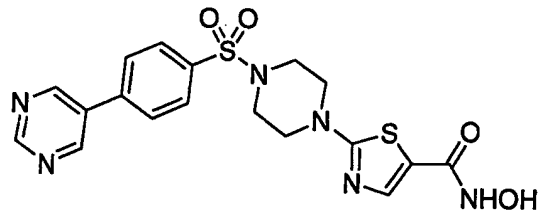
[00403] Same as Example 14.

Example 211

2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00404] Same as Example 15.

Example 291



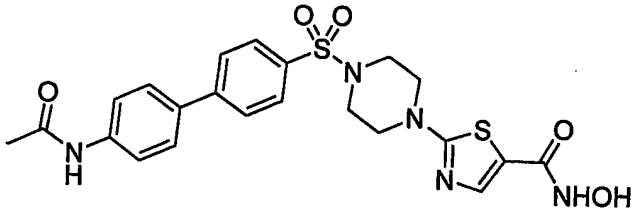
2-[4-{(4-pyrimidine)benzenesulfonyl}-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00405] HPLC: 94.58 % (Rt = 11.98 min);

[00406] ^{1}H NMR (CD_3OD, 200 MHz), δ: 9.22 (1H, s), 9.16 (2H, s), 8.01 (4H, s), 7.75 (1H, bs), 3.69 (4H, m) 3.24 (4H, m);

[00407] MS (*m/z*) 447 (M+1).

Example 292



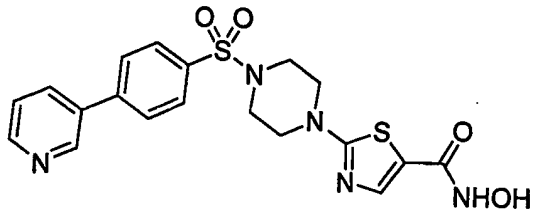
2-[4-{(4-acetamidophenyl)benzenesulfonyl{-piperazine-1-yl-thiazole-5-carboxylic acid hydroxyamide

[00408] HPLC: 90.18 % (Rt = 12.90 min);

[00409] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.88 (4H, bs), 7.70 (5H, bs), 3.68 (4H, m), 3.22 (4H, m), 2.16 (3H, s);

[00410] MS (*m/z*) 502 (M+1).

Example 293

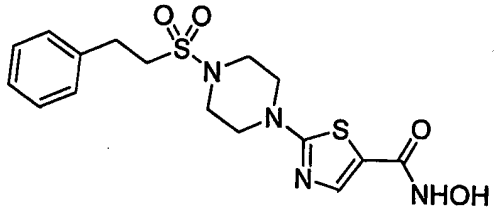


2-[4-{(3-pyrido)benzenesulfonyl}-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00411] HPLC: 93.06% (Rt = 11.23 min);

[00412] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.93 (1H, s), 8.65 (1H, d, J= 4.8Hz), 8.22 (1H, m), 7.98 (4H, bs), 7.73 (1H, m), 7.61 (1H, m), 3.71 (4H, m), 3.24 (4H, m); MS (*m/z*) 446 (M+1).

Example 294



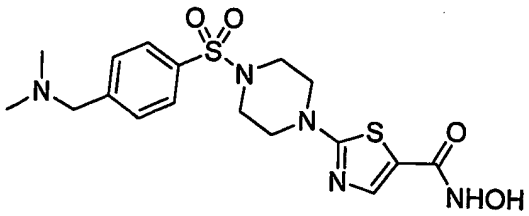
2-[4-(phenethylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00413] HPLC: 97.63 % (Rt = 13.41 min);

[00414] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.81 (1H, bs), 7.31 (5H, m), 3.74 (4H, m), 3.53 (4H, m), 3.45 (2H, m), 3.13 (2H, m);

[00415] MS (*m/z*) 397 (M+1).

Example 295

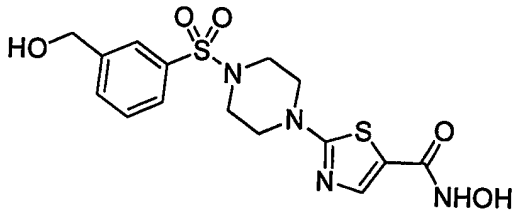


2-[4-(4-N,N-dimethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00416] HPLC: 71.37 (Rt = 11.17min);

[00417] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.00-7.79 (5H, m), 4.43 (2H, s), 3.81 (4H, m), 3.37 (4H, m), 2.95 (6H, s); MS (*m/z*) 426 (M+1).

Example 296

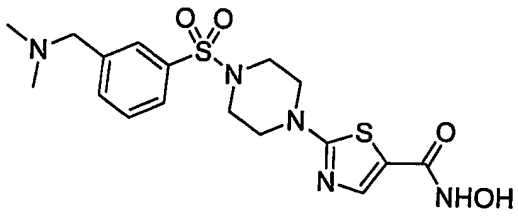


2-[4-(4-hydroxymethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00418] HPLC: 84.57 % (Rt = 11.41 min);

[00419] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.82 (1H, bs), 7.66 (4H, m), 4.72 (2H, s), 3.66 (4H, m), 3.16 (4H, m); MS (*m/z*) 399 (M+1).

Example 297



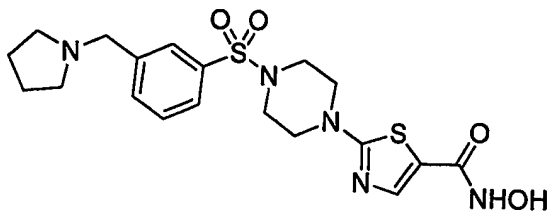
2-[4-(3-N,N-dimethylaminobenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00420] HPLC: 80.24% (Rt 10.91 min);

[00421] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.93-7.71 (5H, m), 4.08 (2H, s), 3.68 (4H, m), 3.18 (4H, m), 2.62 (6H, s);

[00422] MS (*m/z*) 426 (M^+, 100.00).

Example 298



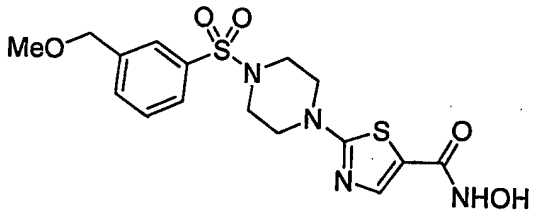
2-[4-(3-pyrrolidonobenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00423] HPLC: 99.21% (Rt = 11.13 min);

[00424] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.82-7.60 (5H, m), 3.76 (2H, s), 3.65 (4H, m), 3.16 (4H, m), 2.58 (4H, m), 1.83 (4H, m);

[00425] MS (*m/z*) 452 (M+1).

Example 299



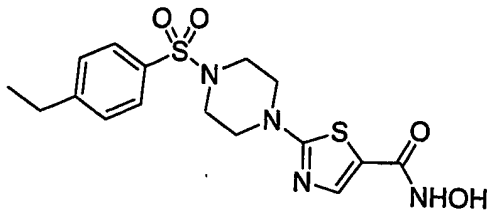
2-[4-(3-methoxymethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00426] HPLC: 93.25 % (Rt = 12.71 min);

[00427] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.79-7.60 (5H, m), 4.57 (2H, s), 3.56 (4H, m), 3.44 (3H, s), 3.15 (4H, m);

[00428] MS (*m/z*) 413 (M+1).

Example 300



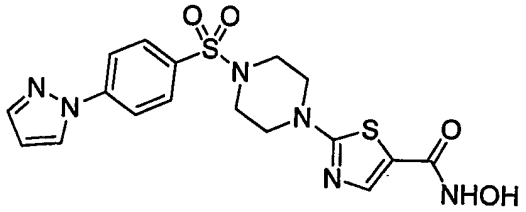
2-[4-(4-Ethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00429] HPLC: 96.32 % (R = 14.02 min);

[00430] ^{1}HNMR (CD_3OD, 200 MHz), δ: 7.73 (3H, m), 7.48 (2H, m), 3.66 (4H, m), 3.14 (4H, m), 2.77 (2H, q, J = 7.4 Hz), 1.28 (3H, t, J = 7.5 Hz);

[00431] MS (m/z): 396 (M+1)

Example 3 01



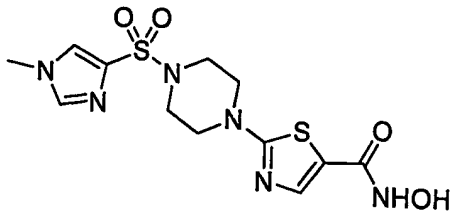
2-[4-(4-pyrazolylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00432] HPLC: 93.63 % (Rt = 12.87 min);

[00433] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.20 (1H, s), 8.13 (2H, d, *J* = 8.5Hz), 7.91 (2H, d, *J* = 8.5Hz), 7.81 (1H, s), 7.52 (1H, m), 6.64 (1H, s), 3.79 (4H, m), 3.27 (4H, m);

[00434] MS (*m/z*) 435 (M+1).

Example 302



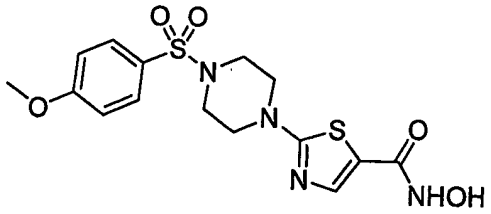
2-[4-(1-methyl-imidazol-4-yl-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00435] HPLC: 96.97 % (Rt = 7.69 min);

[00436] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.74 (1H, s), 8.16 (1H, s), 7.78 (1H, bs), 3.95 (3H, s), 3.87 (4H, m), 3.42 (4H, m);

[00437] MS (*m/z*) 373 (M+1).

Example 303



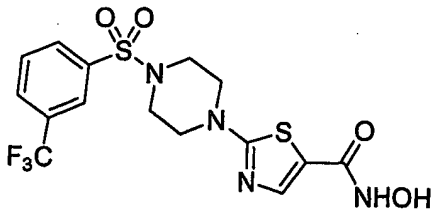
2-[4-(4-Methoxybenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00438] HPLC 88.16 % (Rt = 14.96 min);

[00439] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.79 (3H, m), 7.17 (2H, d, J = 9.2 Hz), 3.90 (3H, s), 3.76 (4H, m), 3.28 (4H, m);

[00440] MS (*m/z*) 399 (M+1).

Example 304



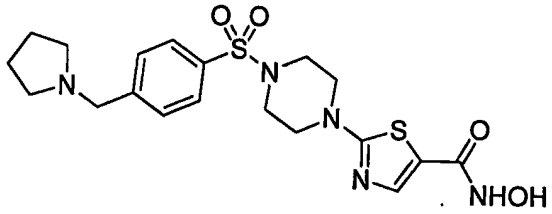
2-[4-(4-Trifluoromethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00441] HPLC: 95.02% (Rt = 16.12 min);

[00442] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.11 (3H, m), 7.92 (2H, m), 3.78 (4H, m), 3.23 (4H, m);

[00443] MS (*m/z*) 437 (M+1).

Example 305



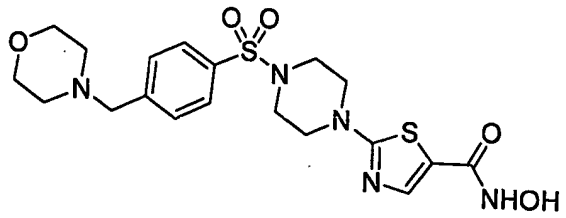
2-[4-(4-Pyrrolidinobenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00444] HPLC: 91.98 % (Rt = 11.05 min);

[00445] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.97-7.82 (5H, m), 4.52 (2H, s), 3.83-3.77 (4H, m), 3.60 (2H, m), 3.34-3.18 (6H, m), 2.22-2.05 (4H, m);

[00446] MS (*m/z*) 451 (M+1).

Example 306



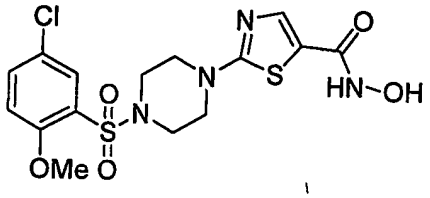
2-[4-(4-Morpholinibenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00447] HPLC: 91.80 % (RT 10.89 min);

[00448] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.95 (3H, m), 7.85 (2H, d, J = 7.2Hz), 4.51 (2H, s), 4.05 (2H, m), 3.87-3.71 (6H, m), 3.49-3.22 (8H, m);

[00449] MS (*m/z*) 468 (M+1).

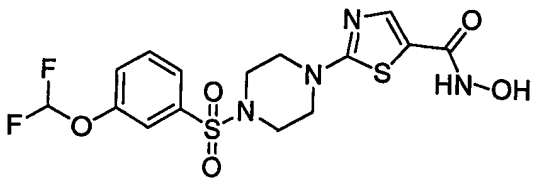
Example 322



2-{4-[(2-chloro-5-methoxyphenyl)sulfonyl]piperazin-1-yl}--1,3-thiazole-5-carboxylic acid hydroxyamide

[00450] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.84 (1H, d. J = 2.2Hz), 7.70 (1H, m), 7.64 (1H, m), 7.26 (1H, d, J = 9.2Hz), 3.96 (3H, s), 3.64 (4H, m), 3.40 (4H, m); MS (*m/e*) = 433 ($M+H^+$).

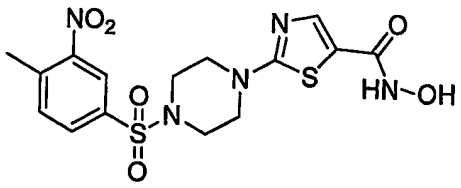
Example 323



2-(4-{[3-(difluoromethoxy)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00451] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.69-7.00 (4H, m), 3.67 (4H, m), 3.24 (4H, m); MS (*m/e*) = 435 ($M+H^+$).

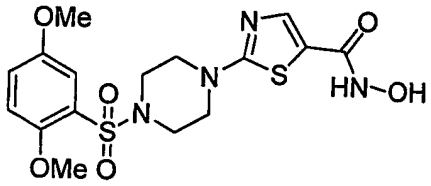
Example 324



2-{4-[(4-methyl-3-nitrophenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00452] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.34 (1H, d. J = 1.4Hz), 8.00 (1H, dd, J = 8.0, 1.4 Hz), 7.75 (1H, d, J = 8.0 Hz), 7.70 (1H, m), 3.68 (4H, t, J = 5.6Hz), 3.22 (4H, t, J = 5.6Hz), 2.67 (3H, s); MS (*m/e*) = 428 ($M+H^+$).

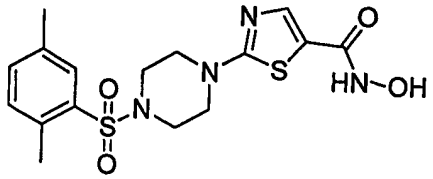
Example 325



2-{4-[(2,5-dimethoxyphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00453] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.84 (1H, m), 7.40 (1H, m), 7.12 (2H, m), 3.90 (3H, s), 3.82 (3H, s), 3.63(4H, m), 3.37 (4H, m); MS (*m/e*) = 429 ($M+H^+$).

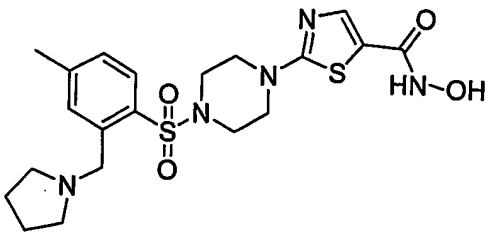
Example 326



2-{4-[(2,5-dimethylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00454] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.75 (2H, m), 7.38-7.36 (2H, m), 3.64 (4H, m), 3.39 (4H, m), 2.60 (3H, s), 2.40 (3H, s); MS (*m/e*) = 397 (M = H^+).

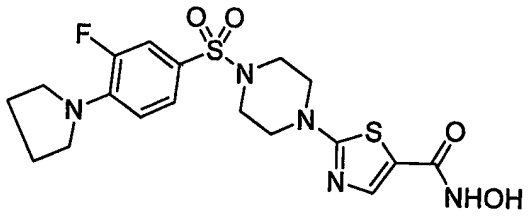
Example 327



2-(4-{[2-(pyrrolidin-1-ylmethyl)-4-methylphenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00455] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.71 (4H, m), 4.34 (2H, m), 3.67 (4H, m), 3.34 (4H, m), 3.24 (4H, m), 2.07 (4H, m); MS (*m/e*) = 466 (M + H^+).

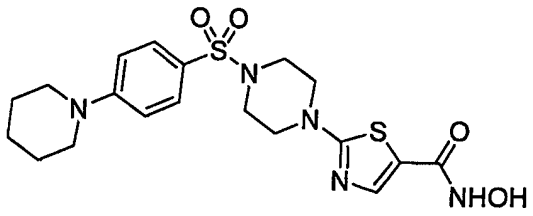
Example 328



2-(4-{[3-fluoro-4-(pyrrolidin-1-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00456] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.71(1H, m), 7.40 (2H, m), 6.85 (1H, m), 3.65 (4H, m), 3.54 (4H, m), 3.11 (4H, m), 2.00 (4H, m); MS (*m/e*) = 456 (M+H^+).

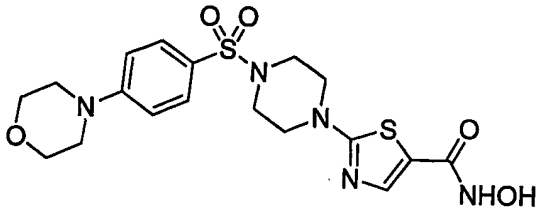
Example 329



2-(4-{[4-(piperidin-1-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00457] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.71 (1H, m), 7.65 (2H, d, J = 9.2 Hz), 7.15 (2H, d, J = 9.2Hz), 3.66 (4H, t, J = 5.2Hz), 3.44 (4H, t, J = 4.8Hz), 3.12 (4H, t, J = 5.4Hz), 1.72 (6H, m); MS (*m/e*) = 452 ($M+H^+$).

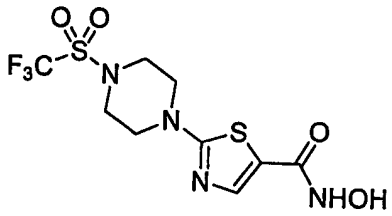
Example 330



2-(4-{[4-(morpholin-4-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00458] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.45 (2H, s), 7.88 (1H, s), 7.65 (2H, d, J = 8.4 Hz), 7.10 (2H, d, J = 8.4Hz), 3.86 (4H, t, J = 5.0Hz), 3.62 (4H, m), 3.24 (4H, m), 3.12 (4H, t, J = 5.6Hz); MS (*m/e*) = 454 ($M+H^+$).

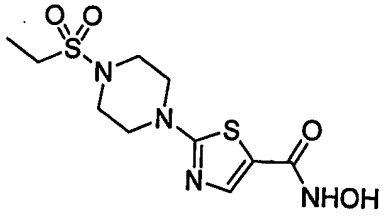
Example 331



2-{4-[(trifluoromethyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00459] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.85 (1H, m), 3.68 (4H, m) 3.34 (4H, m); MS (*m/e*) = 361 ($M+H^+$).

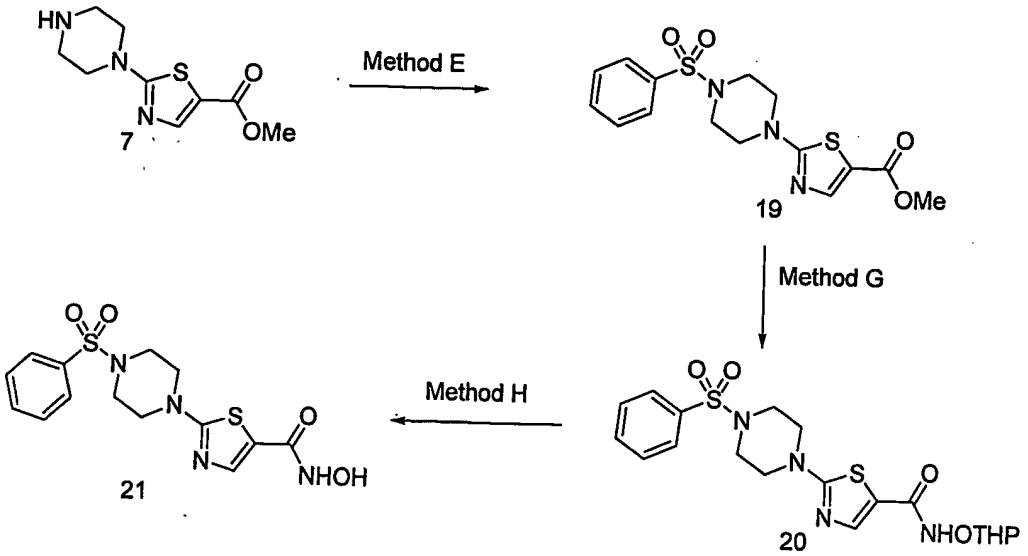
Example 332



2-{4-[ethylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00460] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.79 (1H, bs), 3.65 (4H, m), 3.42 (4H, m), 3.15 (2H, m), 1.37 (3H, t, J = 7.2Hz); MS (*m/e*) = 321.0 ($M+H^+$).

[00461] The following scheme is referred to, below:



Scheme 17

Example 212

2-[4-(benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

Method E

[00462] To a solution of compound (7) (150 mg, 0.660 mmol) in dichloromethane (7.5mL) were added benzenesulfonyl chloride (133 mg, 0.750 mmol) and triethylamine (146 mg, 2.169 mml) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 4h (progress of the reaction was monitored by TLC analysis). Water (10 ml) followed by dichloromethane (10 ml) were added to the reaction mixture and the organic layer was separated, dried on sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel to give the compound **19** as a solid (190 mg).

[00463] HPLC: 96.50 % (Rt = 15.13 min).

[00464] ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.82 (1H, s), 7.80-7.56 (5H, m), 3.81 (3H, s), 3.68 (4H, t, J = 5.2Hz), 3.14 (4H, t, J = 5.2Hz).

Method G:

[00465] To a solution of compound **(19)** (200 mg, 0.545 mmol) in methanol (5 ml) was added a solution of sodium hydroxide (152 mg, 3.81 mmol) in water (5 ml) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture pH was adjusted to neutral by adding 1N HCl and methanol was evaporated on a rotavap. The compound was extracted thrice with ethyl acetate and the combined ethyl acetate layers were dried over sodium sulfate, filtered, concentrated and dried under vacuum for 1h to give the corresponding acid. To the isolated acid (160 mg, 0.453 mmol) in DCM (15 ml) were added EDC (173 mg, 0.907 mmol), HOBt (91 mg, 0.679 mmol), DIEA (112 mg, 0.907mmol) and NH_2OTHP (51 mg, 0.430 mmol) simultaneously under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with water and the compound was extracted thrice with DCM and the combined DCM layers were dried over sodium sulfate, filtered, concentrated and purified over silica gel to give compound **20** (93 mg).

[00466] HPLC: 92.62% (Rt = 14.17 min).

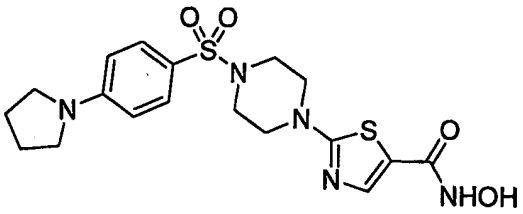
Method H:

[00467] To a solution of compound **20** (93 mg, 0.205 mmol) in MeOH (2mL) were added freshly prepared 20% solution of HCl in ether (10 ml) at 0 °C, and the reaction mixture was stirred at the same temperature for 20 min (progress of the reaction was monitored by HPLC analysis). After complete disappearance of the starting material, solvent was evaporated from the reaction mixture under reduced pressure and the residue was completely dried on high vaccum pump. To the residue was added chilled ether (10 ml) to obtain compound **21** as a white solid (58 mg).

[00468] HPLC: 98.72% (Rt 12.523 min).

[00469] Following the procedures set forth in Example 212 above, the compounds of following examples were prepared using the appropriate starting materials and the ^{1}H NMR data, HPLC and/or mass spectral data are presented below.

Example 213

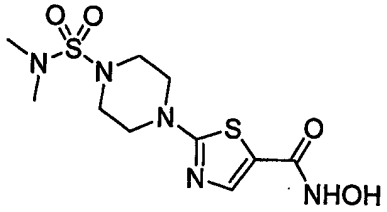


2-[4-(4-pyrolidinylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00470] HPLC: 98.72% (RT 12.523 min);

[00471] MS *m/e*: 438 (M+1).

Example 214



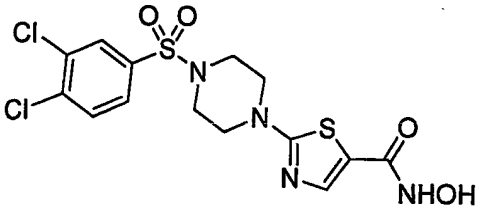
2-[4-(N,N-dimethylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00472] HPLC: 95% (Rt = 10.81 min).

[00473] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.92 (1H, s), 3.77 (4H, t, J = 4.8 Hz), 3.48 (4H, t, J = 4.8 Hz), 2.88 (6H, s);

[00474] MS *m/e*: 336 (M+1).

Example 215

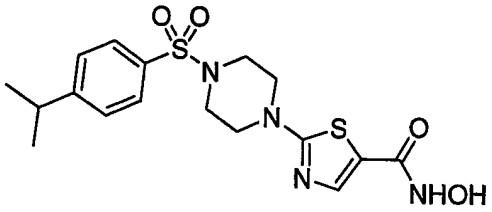


2-[4-(3,4-dichlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00475] HPLC: 94.85 % (Rt = 14.24 min);

[00476] MS *m/e*: 436 (M+1).

Example 216

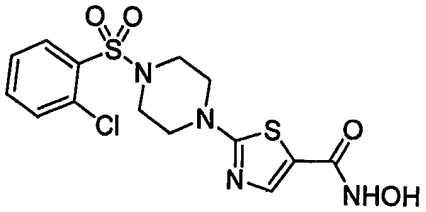


2-[4-(4-*iso*propylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00477] HPLC: 95.14 % (Rt = 14.20 min);

[00478] MS *m/e*: 411 (M+1).

Example 217

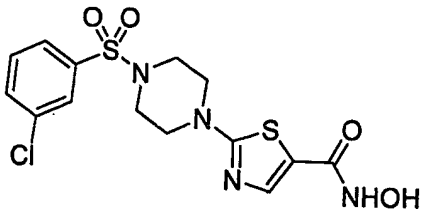


2-[4-(2-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00479] HPLC: 95.66 % (Rt = 13.01 min).

[00480] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.13-7.52 (m, 5H), 3.71 (4H, t, J = 5.4Hz), 3.51(4H, t, J = 5.4Hz); MS *m/e*: 402 (M+1).

Example 218

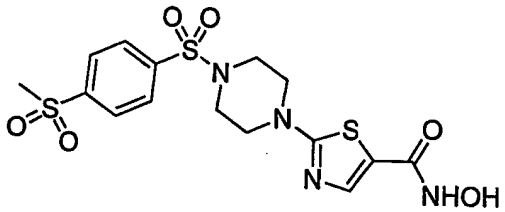


2-[4-(3-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00481] HPLC: 96.91 % (Rt = 13.45 min);

[00482] MS *m/e*: 403 (M+1).

Example 219



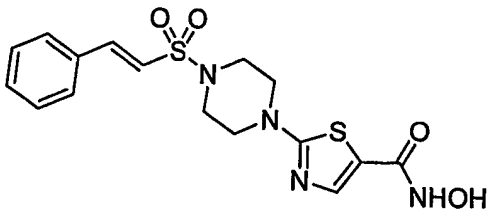
2-[4-(4-methylsufonylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00483] HPLC: 93.09 % (Rt = 12.02 min).

[00484] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.25(2H, d, J = 8.4 Hz), 8.11 (2H, d, J = 8.4 Hz), 7.81 (1H, bs), 3.77 (4H, m), 3.22 (4H, m), 3.21 (3H, s);

[00485] MS *m/e*: 447 (M+1).

Example 220

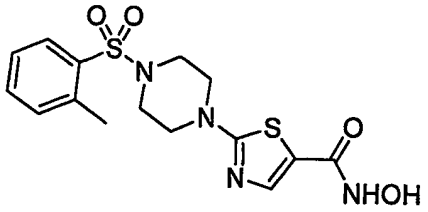


2-[4-(*trans*-2-phenylethanelsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00486] HPLC: 96.66 % (Rt = 13.44 min).

[00487] MS *m/e*: 395 (M+1).

Example 221



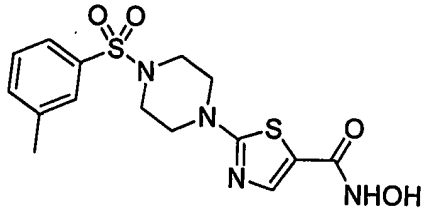
2-[4-(2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00488] HPLC: 90.21 % (Rt = 13.14 min).

[00489] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.92-7.31 (5H, m), 3.77 (4H, t, J = 4.8Hz), 3.48 (4H, t, J = 4.8Hz), 2.88 (3H, s);

[00490] MS *m/e*: 383 (M+1).

Example 222



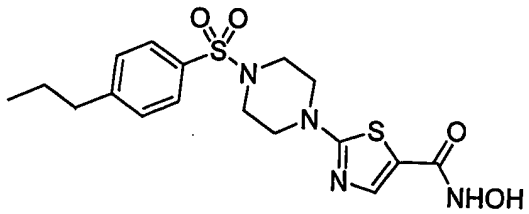
2-[4-(3-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00491] HPLC: 96.27 % (Rt = 13.17 min);

[00492] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.92-7.31 (5H, m), 3.77 (4H, t, J = 4.8 Hz), 3.48 (4H, t, J = 4.8 Hz), 2.88 (3H, s);

[00493] MS (*m/z*) 383 (M+1).

Example 223



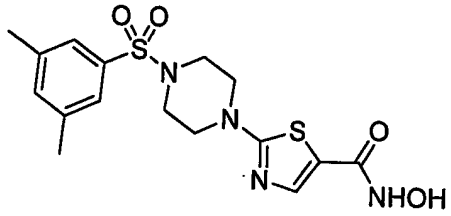
2-[4-(4-*n*-propylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00494] HPLC: 95.53 % (Rt = 14.35 min);

[00495] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.77 (3H, m), 7.50 (2H, d, J = 8.4 Hz) 3.73 (4H, t, J = 4.6 Hz), 3.23 (4H, t, J = 4.6 Hz), 2.72 (2H, t, J = 7.6 Hz), 1.68 (2H, m), 0.98 (2H, t, J = 7.2 Hz);

[00496] MS (*m/z*) 411 (M+1).

Example 224



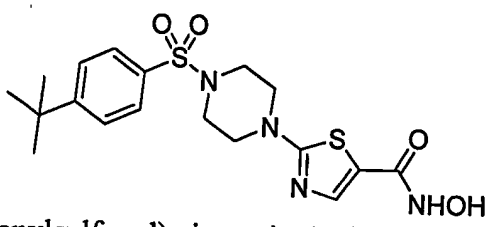
2-[4-(3,5-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00497] HPLC: 94.72 % (Rt = 13.71 min);

[00498] ^{1}H NMR (CD_3OD, 200M Hz), δ: 7.92-7.37 (4H, m), 3.77 (4H, t, J = 4.8 Hz), 3.23 (4H, t, J = 4.8 Hz), 2.42 (6H, s);

[00499] MS (*m/z*) 397 (M+1).

Example 225



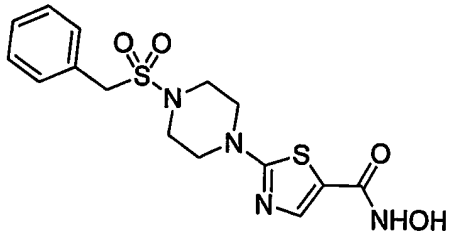
2-[4-(4-t-butylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00500] HPLC: 95.73 % (Rt = 14.62 min);

[00501] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.79-7.67 (5H, m), 3.76 (4H, m), 3.25 (4H, m), 1.34 (9H, s);

[00502] MS (*m/z*) 425 (M+1).

Example 226



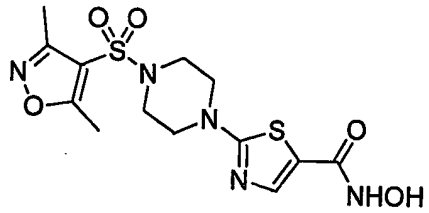
2-[4-(benzylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00503] HPLC: 98.36 % (Rt = 12.72 min);

[00504] ^{1}HNMR (CD_3OD, 200 MHz), δ: 7.83 (1H, m), 7.46-7.39 (5H, m), 4.46 (2H, s), 3.64 (4H, t, J = 4.8 Hz), 3.34 (4H, t, J = 4.8 Hz);

[00505] MS (*m/z*) 383 (M+1).

Example 227



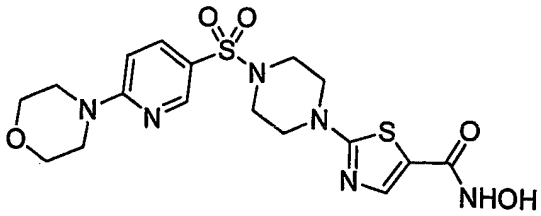
2-[4-(3,5-dimethylisoxazolesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00506] HPLC: 96.54 % (Rt = 12.48 min);

[00507] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.83 (1H, m), 3.78 (4H, bt), 3.37 (4H, bt), 2.69 (3H, s), 2.42 (3H, s);

[00508] MS (*m/z*) 388 (M+1).

Example 228



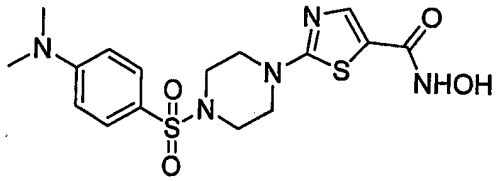
2-[4-({4-morpholino}-3-pyridylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00509] HPLC: 90.72 % (Rt = 11.98 min);

[00510] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.50 (1H, bs), 8.20-7.20 (4H, m), 3.83 (12H, m), 3.33 (4H, m);

[00511] MS (*m/z*) 455 (M+1).

Example 229

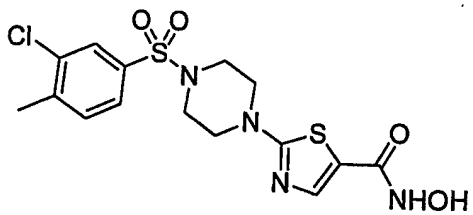


2-[4-(4-dimethylaminophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00512] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 7.8 (bs, 1H, Ar-H), 7.5 (d, J = 8 Hz, 2H, Ar-H), 6.81(d, J = 8 Hz, 2H, Ar-H), 3.54(t, J = 4 Hz, 4H, $2CH_2$), 3.01(s, 6H, $N(Me)_2$), 2.92(t, J = 4 Hz, $2CH_2$).

[00513] MS (m/z) = 412 (M+1).

Example 230



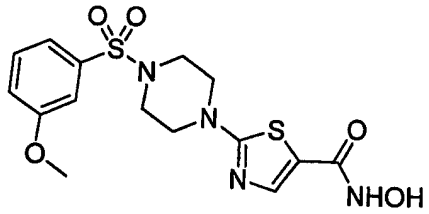
2-[4-(3-chloro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00514] HPLC: 92 % (Rt = 14.31 min).

[00515] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.81 (2H, m), 7.62 (2H, m), 3.81 (4H, m), 3.32 (4H, m), 2.47 (3H, s);

[00516] MS *m/e*: 417 (M+1).

Example 231



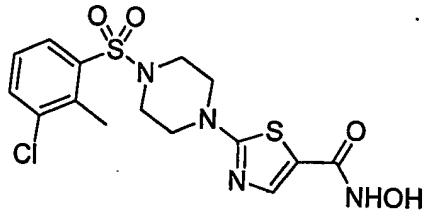
2-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00517] HPLC: 91% (Rt = 13.37 min).

[00518] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.55 (2H, m), 7.33 (3H, m), 3.89 (3H, s), 3.60 (4H, m), 3.32 (4H, m);

[00519] MS *m/e*: 399 (M+1).

Example 232



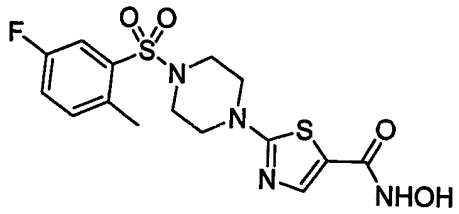
2-[4-(3-chloro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00520] HPLC: 97.4 % (Rt = 14.45 min).

[00521] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.94 (2H, m), 7.75 (1H, m), 7.45 (1H, m), 3.78 (4H, m), 3.48 (4H, m), 2.71 (3H, s);

[00522] MS *m/e*: 417 (M+1).

Example 233



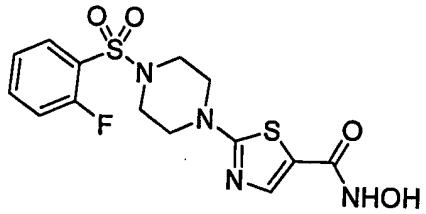
2-[4-(2-methyl-5-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00523] HPLC: 97.5 % (Rt = 13.86 min).

[00524] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.70 (1H, d, J=2.6 Hz), 7.66 (1H, d, *J* = 2.6 Hz), 7.48 (1H, m), 7.35 (1H, m), 3.81 (4H, m), 3.49 (4H, m), 2.62(3H, s);

[00525] MS *m/e*: 401 (M+1).

Example 234



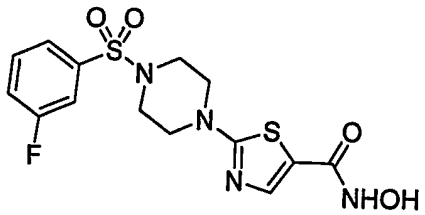
2-[4-(2-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00526] HPLC: 95% (Rt =13.06 min).

[00527] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.90 (2H, m), 7.77 (1H, m), 7.43 (2H, m), 3.78 (4H, m), 3.39 (4H,m);

[00528] MS *m/e*: 387 (M+1).

Example 235



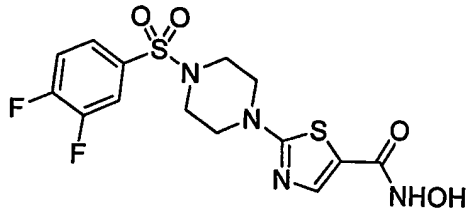
2-[4-(3-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00529] HPLC: 90% (Rt = 13.21 min).

[00530] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.92 (1H, s), 7.65 (2H, m), 7.51 (2H, m), 3.82 (4H, m), 3.34 (4H, m);

[00531] MS *m/e*: 387 (M+1).

Example 236



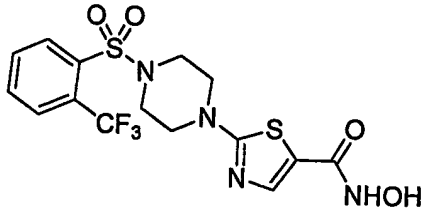
2-[4-(3,4-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00532] HPLC: 82% (Rt = 13.71 min).

[00533] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.83 (2H, m), 7.63 (2H, m), 3.84 (4H, m), 3.33 (4H,m);

[00534] MS *m/e*: 405 (M+1).

Example 237



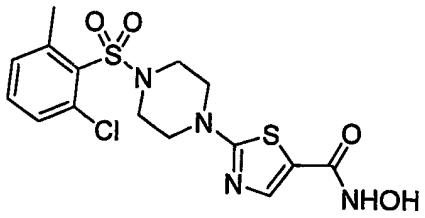
2-[4-(2-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00535] HPLC: 95.03 % (Rt = 13.94).

[00536] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.21 (1H, m),8.04 (1H, m), 7.90 (3H, m), 3.81 (4H, m), 3.53 (4H,m);

[00537] MS *m/e*: 437 (M+1).

Example 238



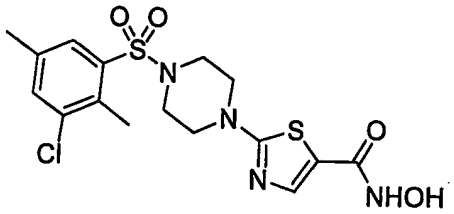
2-[4-(2-methyl-6-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00538] HPLC: 90 % (Rt = 13.89 min).

[00539] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.93 (1H, s), 7.47 (2H, m), 7.40 (1H, m), 3.66 (4H, m), 3.32 (4H, m), 2.74 (3H, s);

[00540] MS *m/e*: 417 (M+1).

Example 239



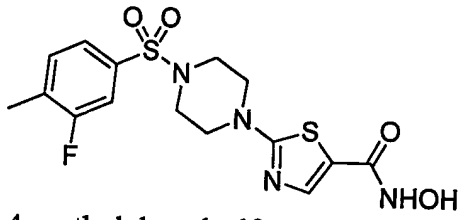
2-[4-(2,5-dimethyl-4-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00541] HPLC: 96.3% (Rt = 15.01 min).

[00542] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.85 (2H, m), 7.48 (1H, m), 3.76 (4H, m), 3.42 (4H, m), 2.59 (3H, s) 2 .43(3H, s);

[00543] MS *m/e*: 431 (M+1).

Example 240



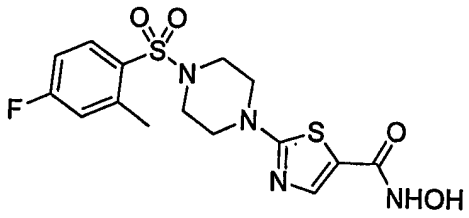
2-[4-(3-fluoro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00544] HPLC: 93% (Rt = 13.90 min).

[00545] ^{1}H NMR (CD_3OD, 200MHz), δ: 7.90 (1H, s), 7.53 (3H, m), 3.77 (4H, m), 3.30 (4H, m), 2.37(3H, s);

[00546] MS *m/e*: 401 (M+1).

Example 241



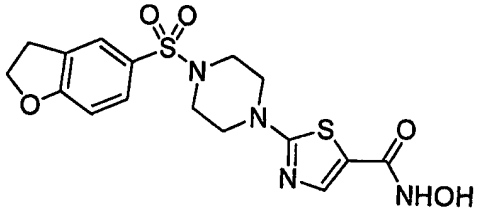
2-[4-(4-fluoro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00547] HPLC: 97.5% (Rt = 13.88 min).

[00548] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.01 (1H, m), 7.92 (1H, s), 7.20 (2H, m), 3.71 (4H, m), 3.43 (4H, m), 2.66(3H, s);

[00549] MS *m/e*: 401 (M+1).

Example 242



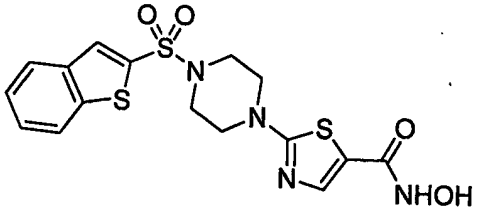
2-[4-(2,3-dihydrobenzofuransulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00550] HPLC: 93.2% (Rt = 13.14 min).

[00551] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.67 (1H, s), 7.63 (1H, d, J = 2.2 Hz), 7.59 (1H, d, J = 2.2 Hz), 4.69 (2H, t, J = 8.8Hz)), 3.81 (4H, m), 3.34 (2H, m), 3.24 (4H, m);

[00552] MS *m/e*: 411 (M+1).

Example 243



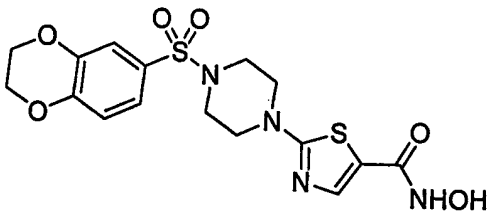
2-[4-(2-benzothiphenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00553] HPLC: 93% (Rt = 14.30 min).

[00554] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.01 (4H, m), 7.54 (2H, m), 3.79 (4H, m), 3.44 (4H, m).

[00555] MS *m/e*: 425 (M+1).

Example 244



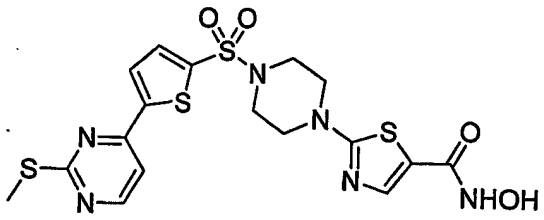
2-[4-(3,4-benzodioxansulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00556] HPLC: 98.8% (Rt = 13.14 min).

[00557] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.30 (2H, m), 7.06 (2H, m), 4.33 (4H, m), 3.75 (4H, m), 3.34 (4H, m);

[00558] MS *m/e*: 427 (M+1).

Example 245



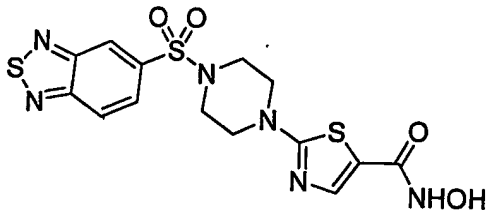
2-[4-(2-{2-methylthiopyrimidine-4-yl}-5-thiophenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00559] HPLC: 96.3% (Rt = 14.31 min).

[00560] ^{1}H NMR (CD_3OD, 200MHz), δ: 8.60 (1H, d, *J* = 5.2Hz), 8.01 (1H, d, J = 4.4 Hz), 7.68 (1H, m), 7.62 (1H, s), 7.59 (1H, s), 3.73 (4H, m), 3.31 (4H, m), 2.62 (3H, s);

[00561] MS *m/e*: 499 (M+1).

Example 246



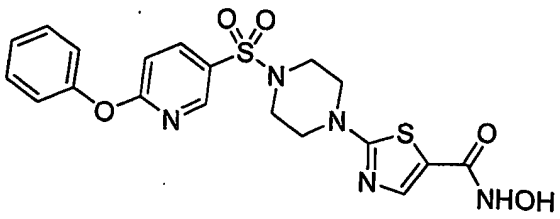
2-[4-(2,1,3-benzothiadiazole-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00562] HPLC: 90.46% (Rt = 16.04 min).

[00563] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.59 (1H, m), 8.24 (1H, m), 8.03 (1H, d, *J* = 1.8Hz), 7.79 (1H, m), 3.72 (4H, m), 3.32 (4H, m);

[00564] MS *m/e*: 427 (M+1).

Example 247



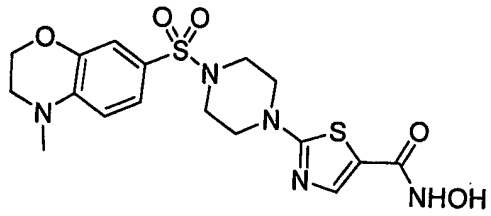
2-[4-(2-phenoxypyridine-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00565] HPLC: 92% (Rt = 14.27 min).

[00566] ^{1}H NMR (CD_3OD, 200 MHz), δ: 8.52 (1H, m), 8.19 (1H, m), 8.15 (1H, m), 7.30 (2H, m), 7.15 (2H, m), 3.68 (4H, m), 3.34(4H, m);

[00567] MS *m/e*: 462 (M+1).

Example 248



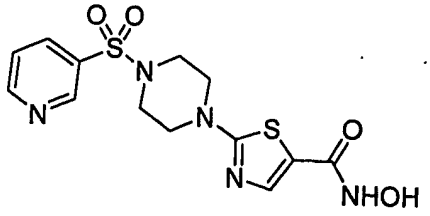
2-[4-(N-methyl-2,3-dihydrobenzisoxazinylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00568] HPLC: 92%.

[00569] ^{1}H NMR (CD_3OD, 300 MHz), δ: 7.62 (s, 1), 6.99-7.03 (dd, J = 1.80, 6.30 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6,84 (d, J = 8.40 Hz, 1H), 4.31 (t, J = 4.8 Hz, 2H), 3.63 (4H, m), 3.34 (4H,m), 3.10 (t, J = 6.0 Hz, 2H), 2.93 (s, 3H);

[00570] MS *m/e*: 440 (M+1).

Example 249

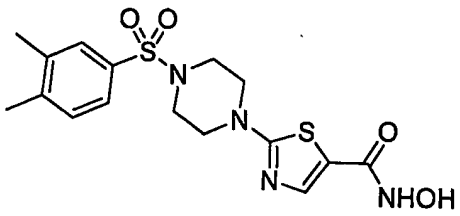


2-[4-(pyridine-3-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00571] ^{1}H NMR (CD_3OD, 300 MHz), δ: 8.88 (m, 2H), 8.20 (m, 1H), 7.68 (m, 2H), 3.56 (m, 2H), 3.12 (m, 2H);

[00572] MS *m/e*: 370 (M+1).

Example 250

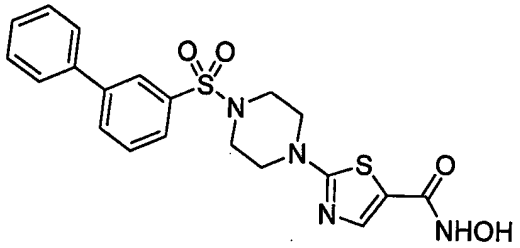


2-[4-(3,4-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00573] ^{1}H NMR (CD_3OD, 300 MHz), δ: 7.74 (s, 1H), 7.53 (m, 2H), 7.37 (m, 1H), 3.63 (m, 4H), 3.10 (m, 4H), 2.36 (s, 6H);

[00574] MS *m/e*: 397 (M+1).

Example 251

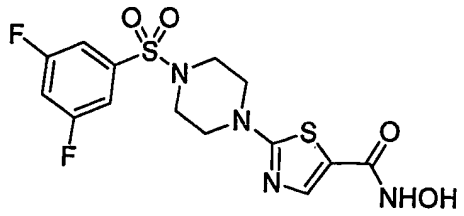


2-[4-(3-biphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00575] ^{1}H NMR (CD_3OD, 300 MHz), δ: 7.90 (m, 2H), 7.75 (m, 6H), 7.42 (m, 2H), 3.63 (m, 4H), 3.26 (m, 4H).

[00576] MS *m/e*: 445 (M+1).

Example 252



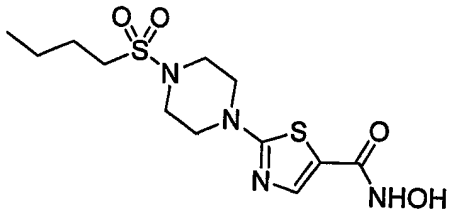
2-[4-(3,5-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00577] HPLC: 91.7 % (Rt = 13.67 min);

[00578] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.8 (1H, hump), 7.46 (2H, m), 7.37 (1H, m), 3.68 (4H, m), 3.22 (4H, m);

[00579] MS (*m/z*) 406 (M+1).

Example 253



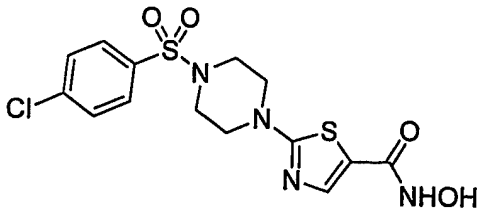
2-[4-(n-butylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00580] HPLC: 96 % (Rt = 12.92 min);

[00581] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.76 (1H, s), 3.67 (4H, m), 3.43 (4H, m), 3.07 (2H, t, J = 6.8Hz), 1.78 (2H, m), 1.49 (2H, m), 1.01 (3H, t, J = 6.8 Hz);

[00582] MS (*m/z*) 349 (M+1).

Example 254



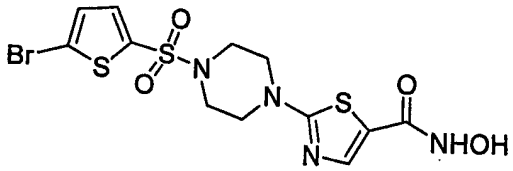
2-[4-(chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide

[00583] HPLC: 98 % (Rt = 14.01 min);

[00584] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.79 (2H, m), 7.66 (3H, m), 3.65 (4H, m) 3.19 (4H, m);

[00585] MS (*m/z*) 403 (M+1).

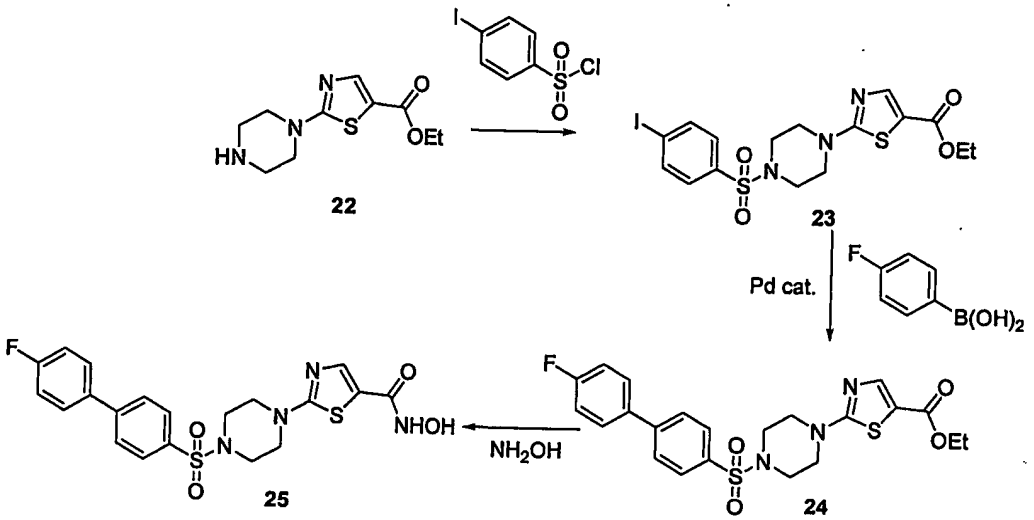
Example 255



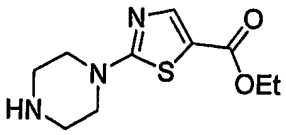
2-{4-[(5-bromothien-2-yl)sulfonyl]piperazin-1-yl}-*N*-hydroxy-1,3-thiazole-5-carboxamide

[00586] White solid (2.5 mg), MS *m/e* 453 ($M+H^+$).

[00587] The following scheme is referred to, below:



Scheme 18



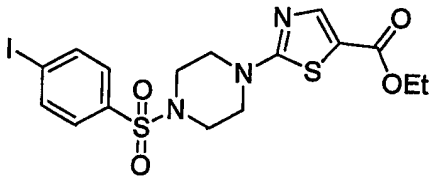
Intermediate 22

[00588] To a solution of piperazine (4.7 g, 0.55 mol) in acetonitrile (60 ml), K_2CO_3 (35 g, 0.25 mol) and ethyl 2-piperazin-1-yl-1,3-thiazole-5-carboxylate (10 g, 42.3 mmol) in acetonitrile (40 ml) were added and refluxed overnight. The reaction mixture was filtered and concentrated in *vacuo*. The residue was taken up in CH_2Cl_2 (40 ml) and this layer was washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated to afford crude intermediate 22. Crude residue was purified using silica gel column (2% MeOH in $CHCl_3$) to obtain pure intermediate 22 (5 g, 49 %).

[00589] $R_f = 0.3$;

[00590] ^1H NMR (400 MHz, $CDCl_3$), δ: 7.86 (s, 1 H), 4.28 (q, $J = 7.1$ Hz, $J =$ 14 Hz, 2 H), 3.52 (t, $J = 5.0$ Hz, 4 H), 2.97 (t, $J = 5.1$ Hz, 4 H). 1.32 (t, $J = 7.1$ Hz, 3 H).

[00591] LCMS (electrospray), *m/e* 242 ($C_{10}H_{15}N_3O_2S + H$).

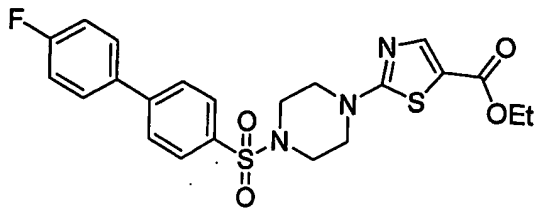


Intermediate 23

[00592] To a solution of intermediate 22 (2.8 g, 11.6 mmol) in CH_2Cl_2 (30 ml) was added triethyl amine (3.2 ml, 23 mmol) and pipsyl chloride (3.9 g, 0.13 mol) over a period of one hour and refluxed for 5 hours. The mixture was diluted with CH_2Cl_2 (50 ml), washed with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified using silica gel column (1% MeOH in $CHCl_3$) to obtain pure intermediate 23 (4.1 g, 69 %).

[00593] $R_f = 0.8$; ^1H NMR (400 MHz, $CDCl_3$), δ: 7.93 (d, $J = 7.8$ Hz, 2 H), 7.48 (d, $J = 7.8$ Hz, 2 H), 4.31 (q, $J = 6.7$ Hz, 2 H), 3.71 (t, $J = 4.8$ Hz, 4 H), 3.16 (t, $J = 4.8$ Hz, 4 H), 1.35 (t, $J = 6.7$ Hz, 3 H).

[00594] LCMS (electrospray), *m/e* 508 ($C_{16}H_{18}IN_3O_4S_2 + H$).



Intermediate 24

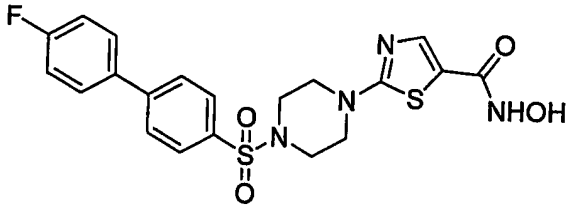
[00595] To a solution of intermediate 23 (0.5 g, 0.99 mmol) in DMF (15 ml, 4-fluorophenylphenylboronic acid (0.276g, 1.97 mmol), palladium acetate (0.066 g, 0.296 mmol), triphenyl phosphine (0.078 g, 0.296 mmol) and cesium carbonate (0.964 g, 2.96 mmol) were added under nitrogen atmosphere and heated at 80°C overnight. The crude material was as such used for column purification (50% EtOAc in petroleum ether) to afford intermediate 24 (0.54 g, 57 %).

[00596] R*f* = 0.6;

[00597] ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.85-7.56 (m, 7 H), 7.22-7.18 (m, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 3.73 (t, *J* = 5.0 Hz, 4H), 3.22 (t, *J* = 5.0 Hz, 4 H), 1.31 (t, *J* = 7.1 Hz, 3 H);

[00598] LCMS (electrospray), *m/e* 476 (M^+ + 1) ($C_{22}H_{22}FN_3O_4S_2$ + H)

Example 256



2-{4-[(4'-fluoro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[Alternative nomenclature: *N*-hydroxy-2-{4-[(4'-fluoro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxamide]

[00599] To a stirred solution of Suzuki coupled intermediate 24 (0.5 g, 0.315 moles) in dioxane (7.0 ml) at 0°C was added hydroxylamine (50% solution in water, 0.2 ml, 3.15 mmol) and the resulting mixture was stirred for 1.0 h at

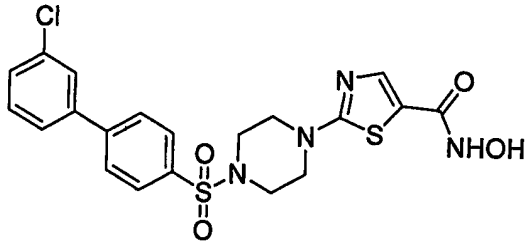
0°C. The reaction mixture was brought to rt and stirred overnight. After removal of dioxane, water (2.0 ml) was added and acidified with 1.5 N HCl. The mixture was concentrated and subjected to preparative HPLC purification to get corresponding hydroxamic acid 14.0 mg (11%).

[00600] ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.95-7.8 (m, 6 H, 6Ar-H), 7.36 (t, 3H, 3Ar-H), 3.67 (d, 4H, $2CH_2$), 3.1 (d, 4H, $2CH_2$).

[00601] LCMS (electrospray), *m/e* 462.8 (M^+) (M, 462.5 Calcd for $C_{20}H_{19}FN_4O_4S_2$)

[00602] Following the procedures set forth in Example 256 above, the compounds of following Examples 257-272 were prepared according to Scheme 18 were prepared using the appropriate starting materials and the ^{1}H NMR data, HPLC and/or mass spectral data are presented below.

Example 257



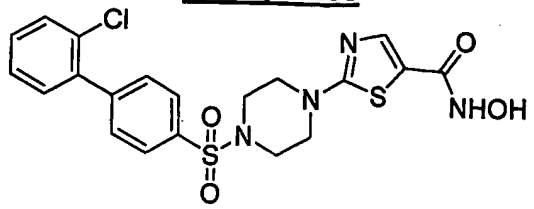
2-{4-[(3'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00603] Yield (35mg, 12%)

[00604] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 7.99 (d, J = 8Hz, 2H, Ar-H), 7.84 (d, J = 8Hz, 2H, Ar-H), 3.55(d, 4H, $2CH_2$), 3.04 (d, 4H, $2CH_2$).

[00605] LCMS electrospray), *m/e* 478.8 (M^+) (M, 478.9 Calcd for $C_{20}H_{19}ClN_4O_4S_2$).

Example 258



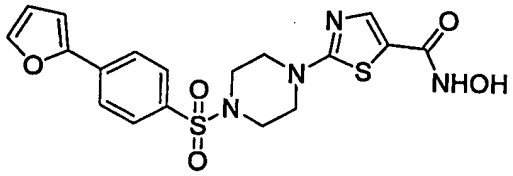
2-{4-[(2'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00606] Yield (35mg, 12%)

[00607] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 7.86 (d, J = 8 Hz, 2H, Ar-H), 7.73 (d, J = 8.3 Hz, 2H, 2Ar-H), 7.64-7.22 (m, 5H, 5Ar-H), 3.6 (t, J = 4.7 Hz, 4H, $2CH_2$), 3.1 (t, J = 4.8Hz, $2CH_2$).

[00608] LCMS (electrospray), *m/e* 478.8 (M+) (M, 478.9 Calcd for $C_{20}H_{19}ClN_4O_4S_2$).

Example 259



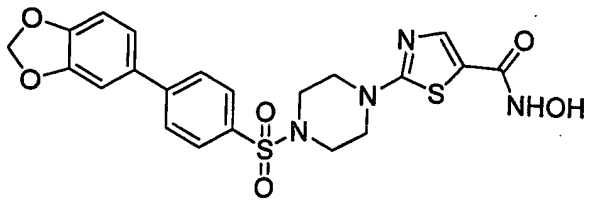
2-(4-{[4-(2-furyl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00609] Yield (17.0 mg, 9%).

[00610] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 7.96-7.65 (m, 5H, 5Ar-H), 7.23-6.68 (m, 3H, 3Ar-H), 3.6 (t, J = 4.1Hz, 4H, $2CH_2$), 3.06 (t, J = 4.7Hz, 4H, $2CH_2$).

[00611] LCMS = 434.8 (M^+) (M, 434.49 Calcd for$C_{18}H_{18}N_4O_5S_2$).

Example 260



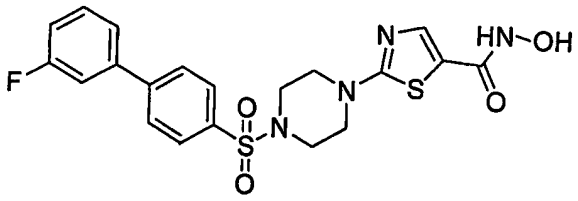
2-(4-{[4-(1,3-benzodioxol-5-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00612] Off-white solid.

[00613] ^{1}H NMR (300 MHz, DMSO-*d6*), δ: 7.87 (2 H, d, *J* = 8.8 Hz), 7.75 (2 H, d, *J* = 8.8 Hz), 7.65 (1 H, bs), 7.34 (1 H, d, *J* = 2.2 Hz), 7.26 (1 H, m), 7.23 (1 H, d, *J* = 2.2 Hz), 7.04 (1 H, s), 7.02 (1 H, s), 6.08 (2 H, s), 3.52-3.60 (4 H, m), 3.03-3.09 (4 H, m);

[00614] LC/MS (electrospray), *m/e* 489 ($C_{21}H_{20}N_4O_6S_2$ + H)

Example 261



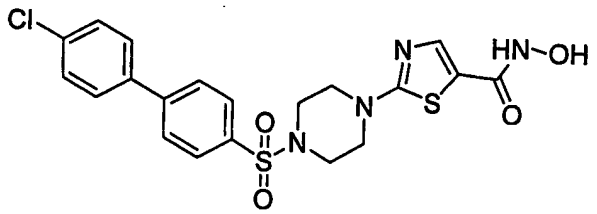
2-{4-[(3'-fluoro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00615] Off-white solid.

[00616] ^{1}H NMR (300 MHz, DMSO-*d6*), δ: 7.97 (2 H, m), 7.81 (2 H, m), 7.49-7.69 (4 H, m), 7.27 (1 H, m), 3.89 (2H, s), 3.11 (4 H, m);

[00617] LC/MS (electrospray), *m/e* 463 ($C_{20}H_{19}FN_4O_4S_2$ + H)$^+$.

Example 262



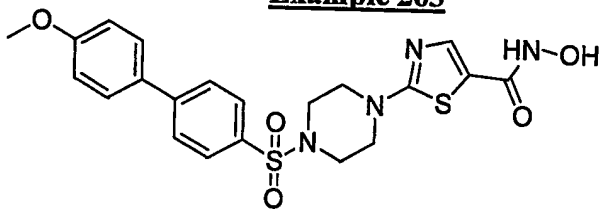
2-{4-[(4'-chloro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00618] Off-white solid.

[00619] ^{1}H NMR (300 MHz, DMSO-*d6*), δ: 7.94 (2 H, d, *J* = 8.4 Hz), 7.7-7.9 (4 H, m), 7.56 (2 H, d, *J* = 8.4 Hz), 5.31 (1 H, s), 2.28 (4 H, m), 3.98 (4 H, m), 2.35 (4 H, m);

[00620] LC/MS (electrospray), *m/e* 479 ($C_{20}H_{19}ClN_4O_4S_2 + H)^+$.

Example 263



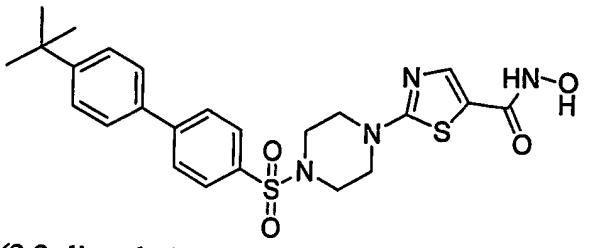
2-{4-[(4'-methoxy-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00621] Off-white solid.

[00622] ^{1}H NMR (300 MHz, DMSO-*d6*), δ: 7.88 (2 H, d, *J* = 8.4 Hz), 7.76 (2 H, d, *J* = 8.4 Hz), 7.69 (2 H, d, *J* = 8.3 Hz), 7.65 (1 H, brs), 7.05 (2 H, d, *J* = 8.3 Hz), 3.83 (3 H, s), 3.57 (4 H, m), 3.06 (4 H, m);

[00623] LC/MS (electrospray), *m/e* 475 ($C_{21}H_{22}N_4O_5S_2 + H)^+$.

Example 264



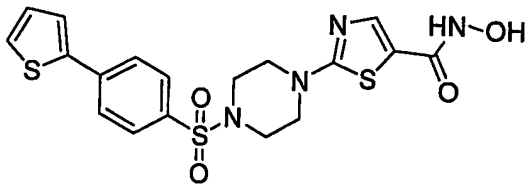
2-{4-[(4'-(2,2-dimethylpropyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00624] Off-white solid.

[00625] ^{1}H NMR (300 MHz, DMSO-*d6*), δ: 7.91 (2 H, d, *J* = 9 Hz), 7.79 (2 H, d, *J* = 9 Hz), 7.66 (2 H, d, *J* = 8.4 Hz), 7.51 (2 H, d, *J* = 8.4 Hz), 3.58 (4 H, m), 3.08 (4 H, m), 1.36 (9 H, s);

[00626] LC/MS (electrospray), *m/e* 501 ($C_{24}H_{28}N_4O_4S_2 + H)^+$.

Example 265



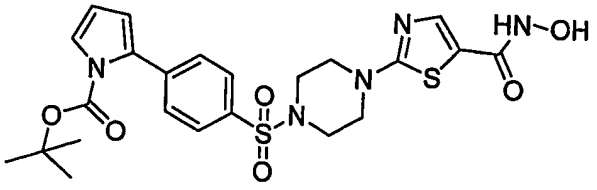
2-{4-[(4-thien-2-ylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxamide

[00627] Off-white solid.

[00628] ^{1}H NMR (300 MHz, DMSO-*d6*), δ: 7.91 (2 H, d, *J* = 7.8 Hz), 7.56-7.82 (5 H, m), 7.19 (1 H, t, *J* = 4.2 Hz), 3.65 (4 H, m), 3.18 (4 H, m);

[00629] LC/MS (electrospray), *m/e* 451 ($C_{18}H_{18}N_4O_4S_3 + H)^+$.

Example 266



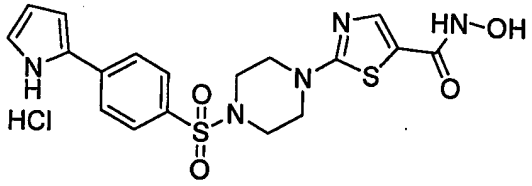
2-(4-{[4-(1-(2,2-dimethylprop-oxycarbonyl)-1*H*-pyrrol-2-yl)phenyl]-sulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00630] Off-white solid:

[00631] ^{1}H NMR (300 MHz, DMSO-*d*6), δ: 7.5-7.8 (5 H, m), 7.41 (1 H, bs), 6.39 (1 H, bs), 6.32 (1 H, t, J = 4.1 Hz), 3.61 (4 H, m), 3.15 (4 H, m), 1.24 (9 H, s);

[00632] LC/MS (electrospray), *m/e* 534 ($C_{23}H_{27}N_5O_6S_2 + H)^+$.

Example 267



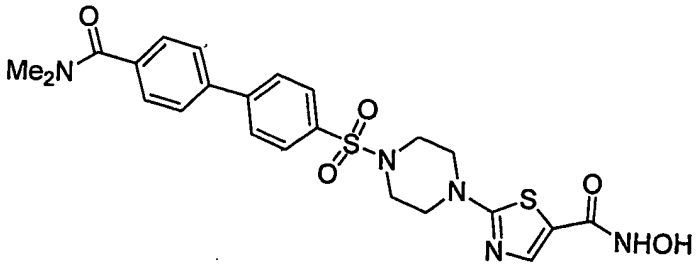
2-(4-{[4-(1*H*-pyrrol-2-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00633] Off-white solid.

[00634] ^{1}H NMR (300 MHz, DMSO-*d*6), δ: 7.83 (2 H, d, J = 8.48 Hz), 7.56-7.78 (3 H, m), 6.96 (1 H, s), 6.72 (1 H, s), 6.17 (1 H, s), 3.56 (4 H, m), 3.04 (4 H, m ;

[00635] LC/MS (electrospray), *m/e* 470 ($C_{18}H_{20}ClN_5O_4S_2 + H)^+$.

Example 268

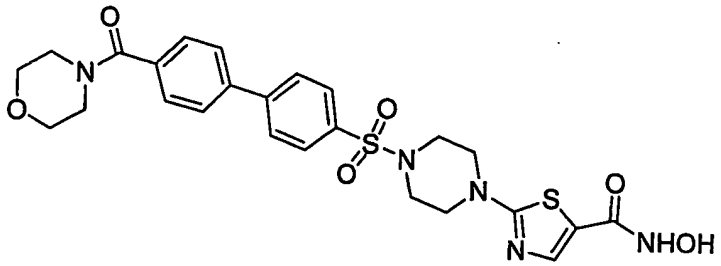


2-[4-(4'-N,N-dimethylcarboxamido-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide

[00636] A white solid (15 mg).

[00637] *m/e* 516 ($M+H^+$).

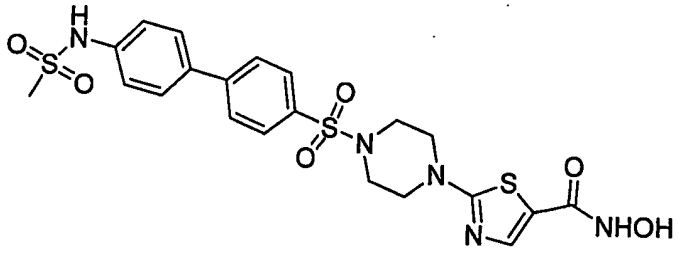
Example 269



2-[4-(4'-(morpholin-4-ylcarbonyl)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide

[00638] ^{1}HNMR DMSO-D6, δ: 3.15 (m, 4H), 3.40-3.65 (m, 6H), 7.50 (d, 2H,), 7.62 (bs, 1H), 7.80 (dd, 4H), 8.0 (d, 2H).

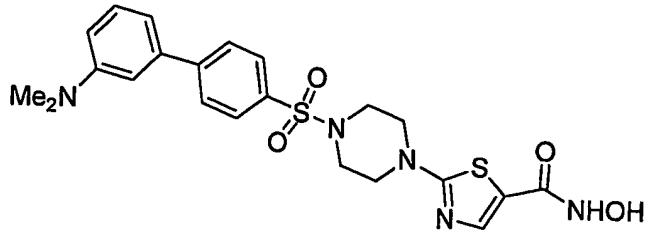
Example 270



2-[4-(4'-methylsulfonylamino-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide

[00639] MS *m/e*: 538 ($M+H^+$).

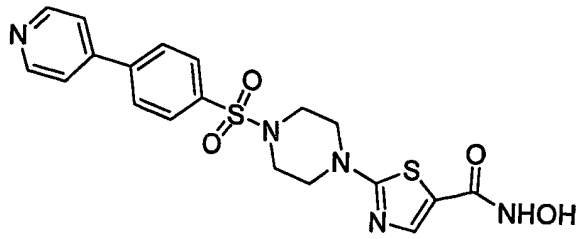
Example 271



2-[4-(3'-(dimethylamino)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide

[00640] (24 mg) M488 ($M+H^+$).

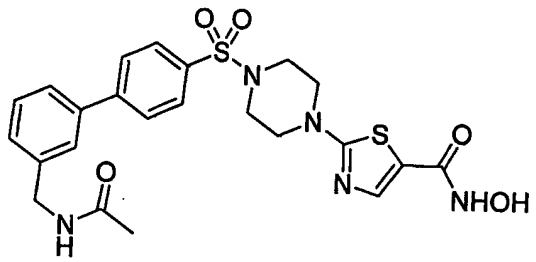
Example 272



2-{4-[4-(pyridin-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00641] ^{1}HNMR DMSO-D6, δ: 3.10 (m, 4H, CH2), 3.60 (bm, 4H, CH2), 7.70 (bs, 1H, olefinic), 8.0 (d, 2H, aromatic), 8.10 (d, 2H, aromatic), 8.15 (d, 2H, aromatic), 8.85 (d, 2H, aromatic), 10.0 (bs, 1H).

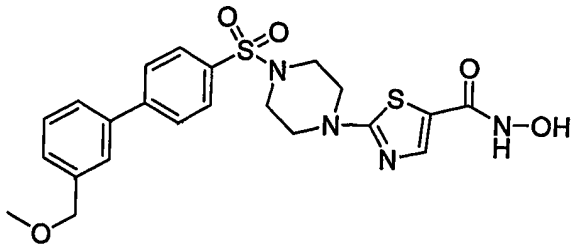
Example 319



2-{4-[3'-{[*N*-acetylamino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00642] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.90-7.39 (9H, m), 4.45 (2H, m), 3.68 (4H, m), 3.20 (4H, m), 2.02 (3H, s); MS (*m/e*) = 516 ($M+H^+$).

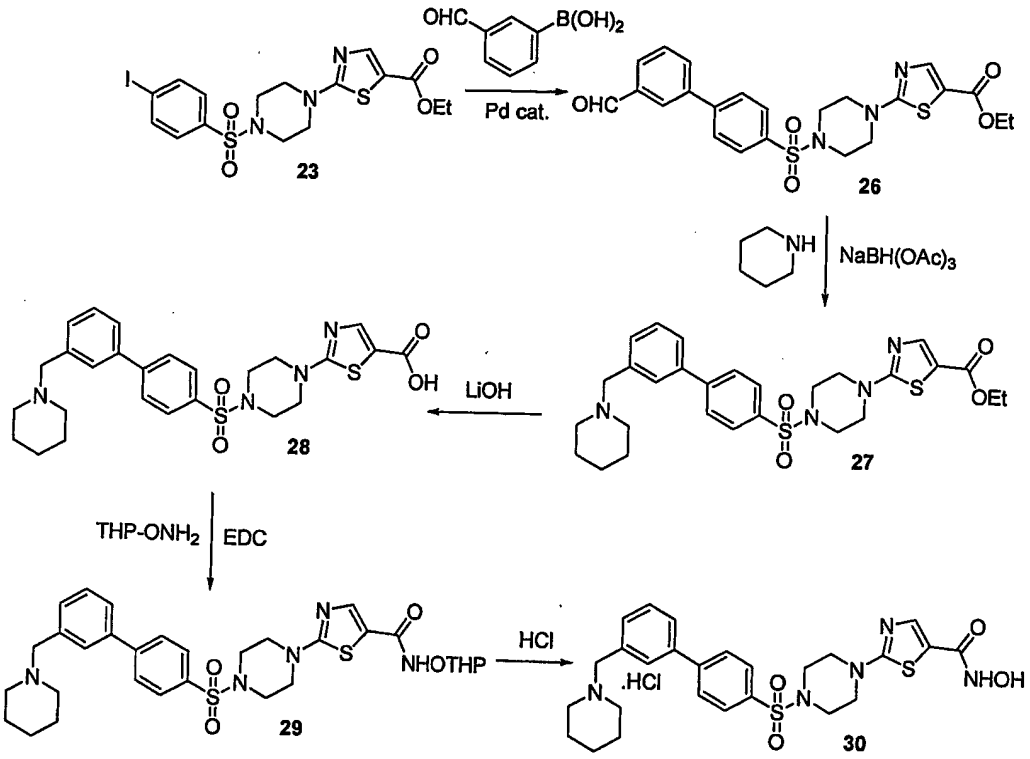
Example 320



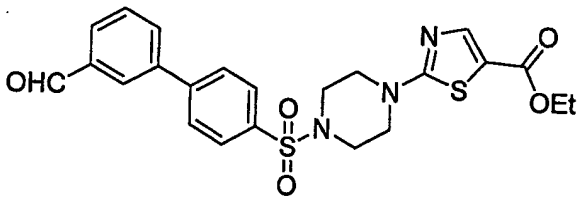
2-{4-[3'-{methoxymethyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00643] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.94 (4H, m), 7.69-7.44 (5H, m), 4.56 (2H, s), 3.68 (4H, m), 3.43 (3H, s), 3.20 (4H, m); MS (*m/e*) = 489.0 ($M + H^+$).

[00644] The following scheme is referred to, below:



Scheme 19



Intermediate 26

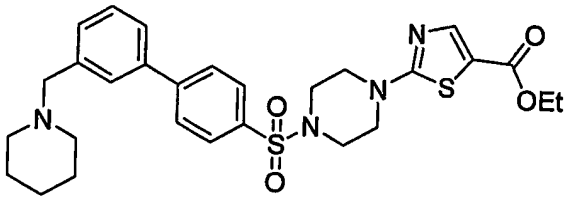
[00645] To a stirred solution of 3-formyl phenyl boronic acid (0.5 g, 0.00333 moles) in THF:water (40 ml:10 ml)) was added iodo intermediate 23 (0.85 g, 0.001675 moles) at rt. After bubbling nitrogen gas in the reaction mixture for 10.0 minutes, freshly prepared tetrakis(triphenylphosphine)palladium (0.184 g, 0.0001674 moles), $CsCO_3$ (4.4g, 0.0135 moles) were added. The reaction mixture was refluxed for 8.0 h. The mixture was concentrated and the residue was partitioned between methylene chloride (100 ml) and water (50 ml). The

layers were separated and the organic layer was washed with brine (25 ml), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified using silica gel column chromatography (5% MeOH in methylene chloride) to give intermediate 26 (0.6g, 74%).

[00646] Rf = 0.8.

[00647] ^1H ($CDCl_3$, 400MHz), δ: 10.12 (s, 1H, CHO), 8.1 (s, 1H, Ar-H), 7.96 (d, J = 8Hz, 1H, Ar-H), 7.88 (d, J = 8Hz, 3H, 3Ar-H), 7.82 (d, J = 8Hz, 3H, 3Ar-H), 2.28 (q, J = 8Hz, 2H, CH2), 3.73 (t, J = 4Hz, 4H, $2CH_2$), 3.22 (t, J = 8Hz, 4H, $4CH_2$), 1.33 (t, J = 8Hz, 3H, CH_3).

[00648] LCMS = 486 (M+ + 1) (M, 485.571 Calcd for $C_{23}H_{23}N_3O_5S$).



Intermediate 27

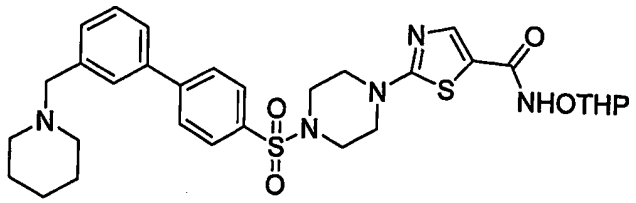
[00649] To a stirred solution of Suzuki coupled intermediate 26 (1.0 g, 0.00206 mol) in dry methylene chloride (50 ml) was added piperidine (0.21 g, 0.00246 mol) and the mixture stirred under N_2 atmosphere. After stirring for 10.0 min, sodium triacetoxy borohydride (0.521 g, 0.00246 mol) was added. The reaction was stirred overnight and treated with 10% $NaHCO_3$ solution (50 ml). The aqueous layer was extracted with methylene chloride (3 x 15 ml). The combined organic layers were washed with brine and concentrated in *vacuo*. The residue was purified using flash silica gel column (1% MeOH in CH_2Cl_2) to give intermediate 27 (580 mg, 85%).

[00650] Rf = 0.5.

[00651] ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.84-7.77 (m, 5H, 5Ar-H), 7.58 (s, 1H, Ar-H), 7.5-7.39 (m, 3H, 3Ar-H), 4.28 (q, J = 8Hz, 2H, CH_2), 3.72 (t, J =

4Hz, 4H, $2CH_2$), 3.56 (s, 2H, CH_2), 3.21 (t, J = 4Hz, 4H, $2CH_2$), 2.42 (bs, 4H, $2CH_2$), 1.6 (m, 4H, $2CH_2$), 1.46 (bs, 2H, CH_2), 1.33 (t, J = 8Hz, 3H, CH_3).

[00652] LCMS = 555 ($M^+ + 1$) (M, 554.726 Calcd for $C_{28}H_{34}N_4O_4S_2$)



Intermediate 29

[00653] Intermediate 27 (0.53 g, 0.000955 mol) was taken in THF+MeOH (50 ml + 50 ml). To the mixture was added NaOH (0.305g, 0.0764 mol) in water (10 ml). After stirring for overnight, it was carefully neutralized with conc. HCl until a pH = 7 was reached. The mixture was concentrated to dryness and crude intermediate 28 (520 mg) was taken as such for the next step.

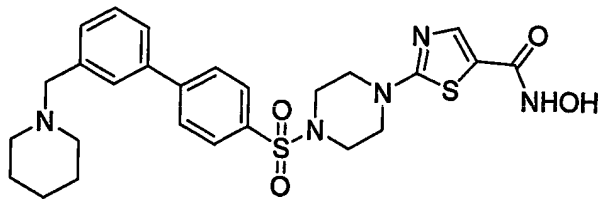
[00654] To a solution of intermediate 28 in DCM (100 ml) was added DIEA (0.37g, 0.002866 mol), HOBt (0.194g, 0.00143 mol), EDC (0.366 g, 0.0019 mol) and NH_2OTHP (0.112 g, 0.000955 mol) in methylene chloride (5 ml). After stirring overnight, water (25 ml) was added and the layers were separated. The aqueous layer was extracted with methylene chloride (3 X 25 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified using flash silica gel column (2% MeOH in methylene chloride) to give intermediate 29 (0.35g, 58%).

[00655] Rf = 0.5.

[00656] ^1H NMR ($CDCl_3$, 400 MHz), δ: 7.84-7.77 (m, 5H, 5Ar-H), 7.60 (bs, 1H, Ar-H), 7.51-7.39 (m, 3H, 3Ar-H), 4.97 (s, 1H, CH), 3.95 (t, J = 4Hz, 4H, $2CH_2$), 3.69 (s, 2H, CH_2), 3.21 (t, J = 4Hz, 4H, $4CH_2$), 2.44 (bs, 4H, $2CH_2$), 1.84 (bs, 4H, $2CH_2$), 1.47 (bs, 8H, $4CH_2$), 1.27 (bs, 2H, CH_2).

[00657] LCMS = 626 ($M^+ + 1$) (M, 625.804 Calcd for $C_{31}H_{39}N_5O_5S_2$).

Example 273



2-{4-[(3'-(piperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

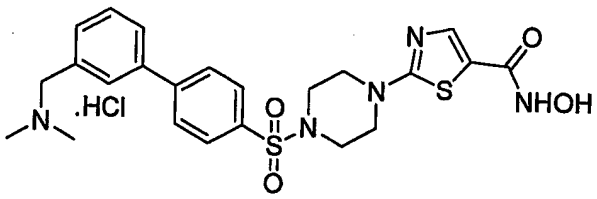
[00658] Intermediate 29 (0.31g, 0.495 mmol) was dissolved in dry MeOH (5 ml) and cooled to 0°C. A saturated solution of HCl in ether (10 ml) was added. After stirring for 3.0 h at 0°C, the reaction was concentrated and the residue was dried. Further purification was done using preparative HPLC to give the title compound (40 mg, 14%).

[00659] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 11.0 (bs, 1H, NH or OH), 10.44 (bs, 1H, OH or NH), 8.07-8.01 (m, 3H, 3Ar-H), 7.85 (m, 3H, 3Ar-H), 7.67-7.58 (m, 3H, 3Ar-H), 4.3 (s, 2H, CH_2), 3.65 (bs, 4H, $2CH_2$), 3.3 (m, 2H, CH_2), 3.08 (bs, 4H, $2CH_2$), 2.8 (m, 2H, CH_2), 1.77-1.35 (m, 6H, $3CH_2$).

[00660] LCMS = 542 ($M^+ + 1$) (M, 578.188 Calcd for $C_{26}H_{32}ClN_5O_4S_2$).

[00661] Examples 274-290 were prepared according to Scheme 19 by the same general procedures described for Example 273 and using the appropriate starting materials.

Example 274



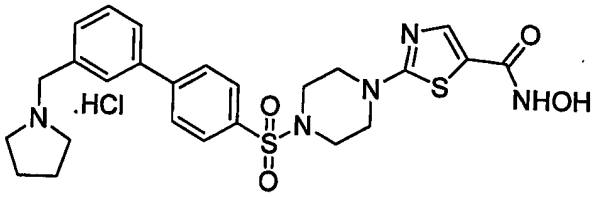
2-{4-[(3'-[(dimethylamino)methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00662] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 10.92 (bs, 1H, NH or OH), 8.06-8.01 (m, 3H, 3Ar-H), 7.85 (m, 3H, Ar-H), 7.69 (bs, 1H, Ar-H), 7.63-7.58 (m, 2H, Ar-H), 4.33 (s, 2H, CH_2), 3.6 (bs, 4H, $2CH_2$), 3.08 (bs, 4H, $2CH_2$), 2.71 (s, 6H, $N(Me)_2$).

[00663] ^{13}C NMR (DMSO-d_6, 100MHz), δ: 144.2, 138.75, 133.93, 131.51, 131.52, 130.09, 129.78, 129.59, 129.26, 128.27, 128.00, 127.85, 127.49, 127.24, 59.25, 47.61, 44.95, 41.52.

[00664] MS *m/e*: 502 (M^+ + 1) (M, 501.124 Calcd for $C_{23}H_{27}N_5O_4S_2$).

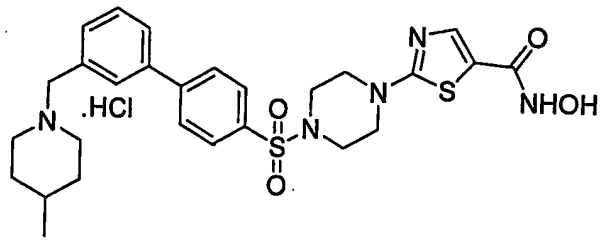
Example 275



2-{4-[(3'-(pyrrolidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00665] ^{1}H NMR(DMSO-d_6, 400 MHz) d = 11.09 (bs, 1H, OH or NH), 8.1 (s, 1H, Ar-H), 8.02(d, 2H, 2Ar-H), 7.87-7.56 (m, 6H, 6Ar-H, 4.42 (s, 2H, CH2), 3.6 (bs, 4H, $2CH_2$), 3.35 (m, 2H, CH_2), 3.07 (bs, 6H, $3CH_2$), 2.02-1.88 (m, 4H, $2CH_2$). MS *m/e*: 528 (M^+ + 1) (M, 527.661 Calcd. for $C_{25}H_{29}N_5O_4S_2$).

Example 276



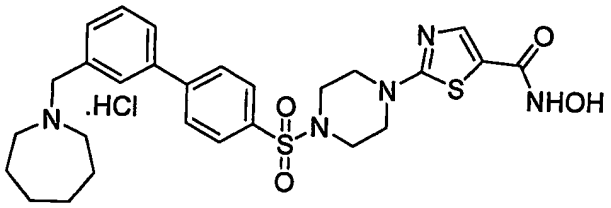
2-{4-[(3'-(4-methylpiperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00666] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 10.91 (bs, 1H, OH or NH), 9.6 (bs, 1H, OH or NH), 7.99-7.85 (m, 6H, 6Ar-H), 7.66 (m, 3H, 3Ar-H), 4.36 (s,

2H, CH_2), 3.59 (bs, 4H, $2CH_2$), 3.34 (d, J = 12 Hz, 2H, CH_2), 3.08 (bs, 4H, $2CH_2$), 2.93 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 1.6 (m, 1H, CH), 1.33 (m, 2H, CH_2), 0.09 (d, J = 8 Hz, 3H, CH_3).

[00667] MS *m/e*: 556 (M^+ + 1) (M, 555.714 Calcd. for $C_{27}H_{33}N_5O_4S_2$).

Example 277

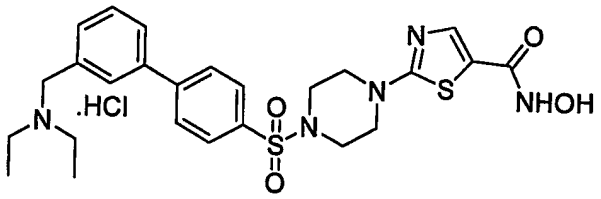


2-{4-[(3'-(hexahydroazepin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00668] ^1H NMR (DMSO-d_6, 400 MHz), δ: 11.0 (bs, 1H, OH or NH), 10.01 (bs, 1H, OH or NH), 8.01-7.59 (m, 9H, 9Ar-H), 4.4 (s, 2H, CH_2), 3.59 (bs, 4H, $2CH_2$), 3.08 (bs, 4H, $2CH_2$), 1.84 (m, 4H, $2CH_2$), 1.62 (m, 4H, $2CH_2$).

[00669] MS *m/e*: 556 (M^+ + 1) (M, 555.714 Calcd. for $C_{27}H_{33}N_5O_4S_2$).

Example 278

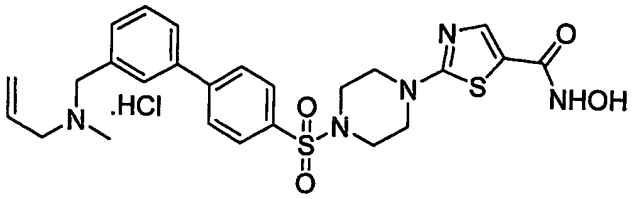


2-{4-[(3'-((diethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00670] ^1H NMR (DMSO-d_6, 400 MHz), δ; 10.5 (bs, 1H, NH or OH), 9.53 (bs, 1H, OH or NH), 7.99-7.59 (m, 9 H, 9 Ar-H), 4.38 (s, 2H, CH_2), 3.59 (bs, 4 H, 2 CH_2), 3.11 (m, 8 H, 4 CH_2), 1.24 (t, J = 8 Hz, 6 H, 2 CH_3).

[00671] MS *m/e*: 530 (M^+ + 1) (M, 529.677 Calcd. for $C_{25}H_{31}N_5O_4S_2$).

Example 279

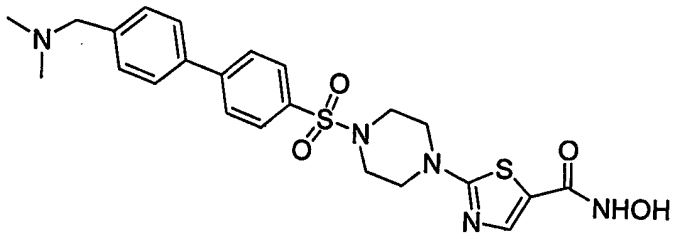


2-{4-[(3'-((methyl(3-propenyl)amino)methyl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00672] ^{1}H NMR (DMSO-d_6, 400 MHz), δ: 10.6 (bs, 1H, OH or NH), 10.7 (bs, 1H, OH or NH), 8.03 (m, 3H, 3Ar-H), 7.88 (m, 3H, 3Ar-H), 7.62 (m, 3H, 3Ar-H), 6.05 (m, 1H, =CH), 5.55 (m, 2H, =CH_2), 4.43 (m, 1H, CH), 4.27 (m, 1H, CH), 3.7 (m, 2H, CH_2), 3.5 (bs, 4H, 2CH_2), 3.08 (bs, 4H, 2CH_2), 2.6 (s, 3H, CH3).

[00673] MS *m/e*: 527 (M^+ + 1) (M, 527.161 Calcd for $C_{25}H_{29}N_5O_4S_2$).

Example 280



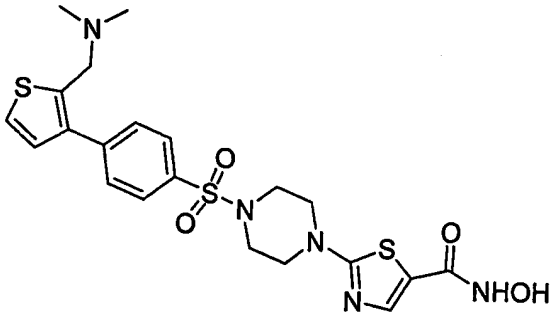
2-{4-[(4'-((dimethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00674] White solid (36 mg), 39% yield.

[00675] *m/e* 502 ($M+H^+$).

[00676] ^{1}HNMR DMSO-D6, δ: 2.8 (s, 6H), 3.1 (bm, 4H), 3.6 (bm, 4H), 4.3 (s, 2H) 7.55-8 (bm, 9H), 9 (bs, 1H), 10.0 (bs, 1H).

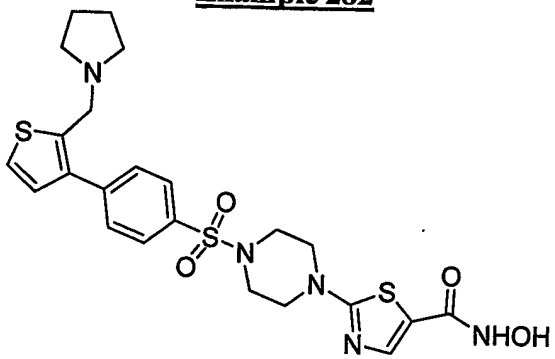
Example 281



2-(4-{4-[(2-((dimethylamino)-methyl)thien-3-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00677] Gum, *m/e* 508 ($M+H^+$).

Example 282



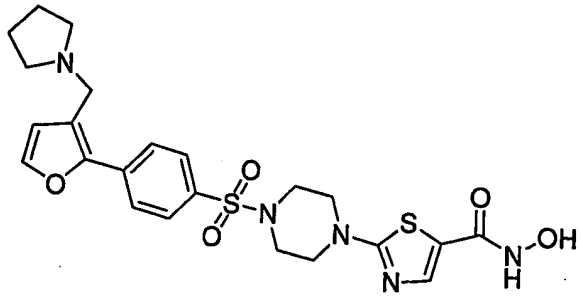
2-(4-[4-{(2-(pyrrolidin-1-ylmethyl)-thien-3-yl)phenylsulfonyl}]piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00678] White solid.

[00679] ^{1}HNMR DMSO-D6, δ: 1.88 (m, 4H), 2.9 (m, 2H), 3.08 (m, 4H), 3.35-3.8 (m, 6H), 4.63 (m, 2H), 7.24 (d, 1H), 7.69 (m, 3H), 7.83 (m, 3H), 9.85 (bs, 1H),

[00680] *m/e* 535 ($M+H^+$).

Example 283



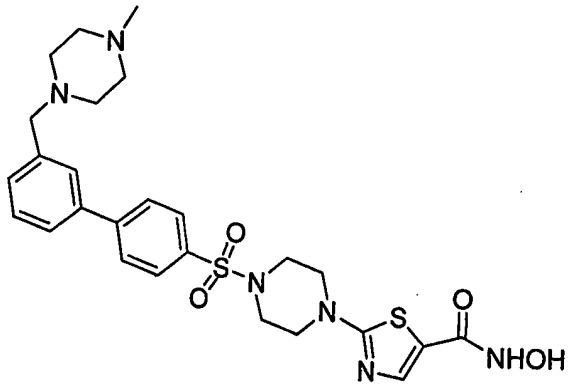
2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00681] White solid.

[00682] H^1NMR DMSO-d_6, δ: 1.85 (m, 2H), 1.99 (m, 2H), 3.08 (m, 8H), 3.58 (m, 4H), 4.52 (d, 2H), 6.86 (d, 1H), 7.74 (m, 1H), 7.8-7.92 (m, 5H), 9.85 (bs, 1H),

[00683] *m/e* 535 ($M+H^+$).

Example 284



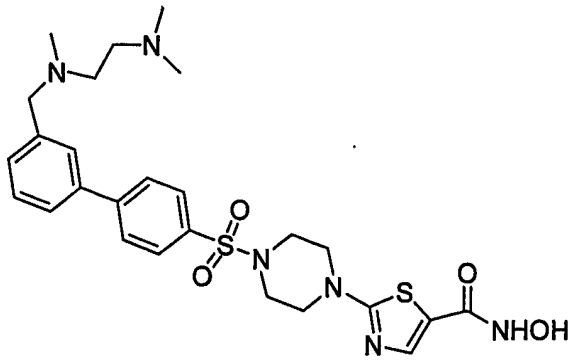
2-{4-[(3'-((4-methylpiperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00684] Floculant white solid (6 mg),

[00685] *m/e* 557 ($M+H^+$)

[00686] ^{1}HNMR DMSO-d6, δ: 2.78 (m, 3H), 3.0-4 (m, 18H), 7.43 (d, 1H), 7.52 (t, 1H), 7.65 (bs, 1H), 7.72 (d, 2H), 7.83 (d, 2H), 7.93 (d, 2H).

Example 285



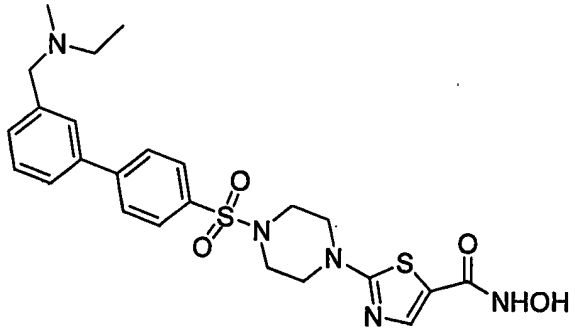
2-{4-[3'-{[(2-(dimethylamino)ethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00687] Floculant white solid (6 mg),

[00688] *m/e* 557 ($M+H^+$).

[00689] ^{1}HNMR DMSO-d_6, δ: 2.81 (m, 9H), 3.0-4 (m, 14H), 7.6-7.82 (m, 5H), 7.85 (d, 2H), 7.95 (d, 2H).

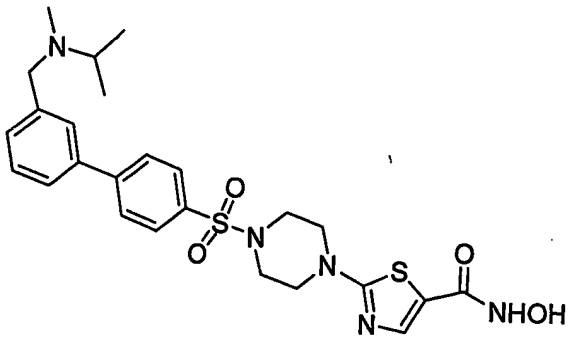
Example 286



2-{4-[(3'-[ethyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00690] Floculant white solid (7 mg), *m/e* 516 ($M+H^+$).

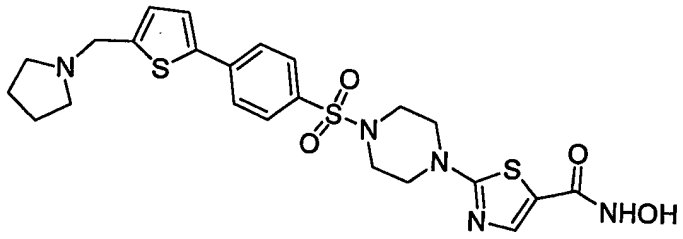
Example 287



2-{4-[(3'-[isopropyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00691] Floculant white solid (6 mg), *m/e* 530 ($M+H^+$).

Example 288



2-(4-{4-[(5-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

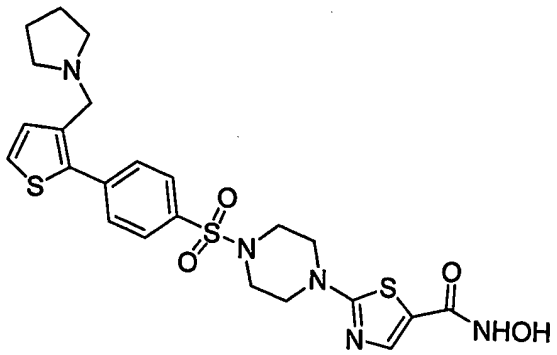
[00692] Floculant white solid (3 mg),

[00693] *m/e* 535 ($M+H^+$),

[00694] ^{1}HNMR DMSO-d_6, δ: 1.88 (m, 2H), 2.05 (m, 2H), 3.1 (m, 8H), 3.6 (m, 4H), 4.65 (m, 2H), 7.38 (m, 1H), 7.65 (m, 2H), 7.78 (d, 2H), 7.9 (d, 2H), 9.95 (bs, 1H), 10.85 (bs, 1H),

[00695] *m/e* 535 ($M+H^+$).

Example 289.



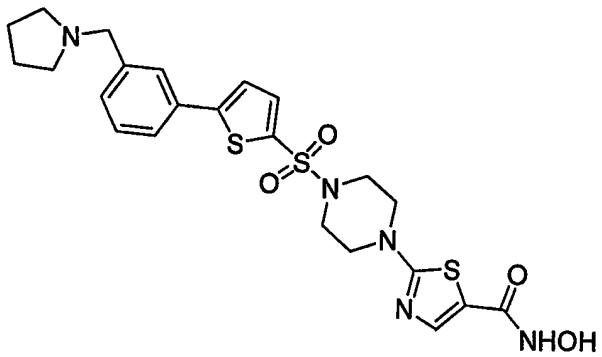
2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00696] Floculant white solid (8 mg),

[00697] *m/e* 535 ($M+H^+$).

[00698] ^{1}HNMR DMSO-d_6, δ: 1.80 (m, 4H), 3.85 (m, 2H), 3.1 (m, 4H), 3.4 (m, 2H), 3.65 (m, 4H), 4.45 (d, 2H), 7.38 (d, 1H), 7.66 (bm, 1H), 7.73 (d, 2H), 7.81-7.88 (m, 3H), 7.9 (d, 2H), 9.95 (bs, 1H), 10.85 (bs, 1H), *m/e* 535 ($M+H^+$).

Example 290



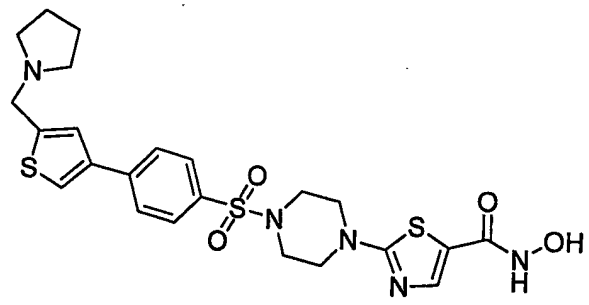
2-(4-{5-[3-(pyrrolidin-1-ylmethyl)phenyl]thiophene-2-sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00699] Floculant white solid (3.5 mg),

[00700] *m/e* 534 ($M+H^+$).

[00701] ^{1}HNMR DMSO-d_6, δ: 1.85 (m, 2H), 2.08 (m, 2H), 3.15 (m, 8H), 3.68 (m, 4H), 4.4 (m, 2H), 7.5-7.9 (m, 2H), 7.66 (bm, 1H), 7.71 (m, 2H), 7.86 (m, 1H) 7.91 (s, 1H), 9.95 (bs, 1H), 10.9 (bs, 1H), *m/e* 534 ($M+H^+$).

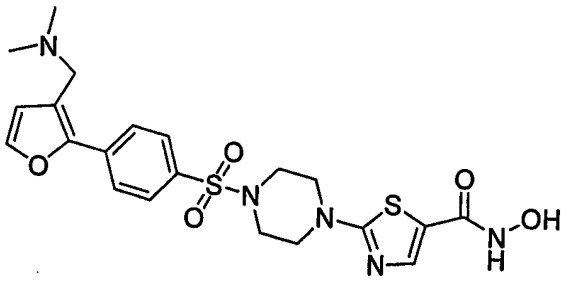
Example 307



2-{4-[4-(2-(pyrrolidin-1-ylmethyl)-thien-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00702] Floculant white solid, m/e = 534 ($M + H^+$), ^{1}HNMR (DMSO-d_6), δ: 2.0 (m, 4H), 3.05 (m, 4H), 3.17 (m, 4H), 3.57 (m, 4H), 4.62 (d, 2H), 7.64 (m, 1H), 7.78-7.81 (m, 3H), 7.95 (d, 2H), 8.23 (m, 1H), 10 (bs, 1H), 10.9 (bs, 1H).

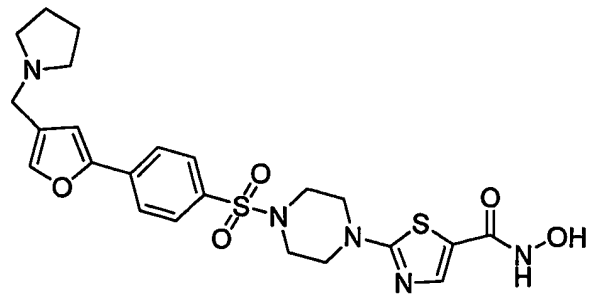
Example 308



2-(4-{4-[3-((dimethylamino)-methyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00703] Floculant yellow solid, m/e = 492 ($M + H^+$), ^{1}HNMR (DMSO-d_6), δ: 2.77 (m, 6H), 3.08 (m, 4H), 3.53 (m, 4H), 4.47 (m, 2H), 6.83 (d, 2H), 7.65 (bs, 1H), 7.83 (d, 2H), 7.91 (d, 2H), 7.97 (d, 1H), 9.9 (bs, 1H), 10.9 (bs, 1H).

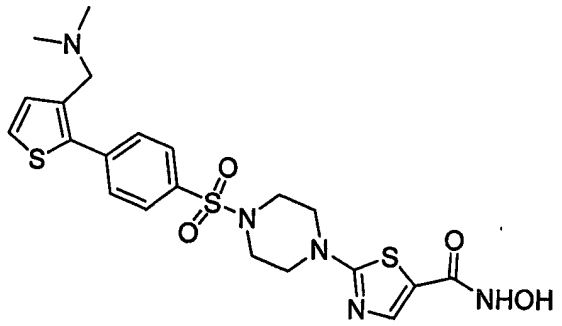
Example 309



2-(4-{4-[(4-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00704] Tan solid, m/e = 518 ($M + H^+$), ^{1}HNMR (DMSO-d_6), δ: 2.0 (m, 4H), 3.1 (m, 8H), 3.6 (m, 4H), 4.25 (d, 2H), 7.3 (s, 1H), 7.65 (bs, 1H), 7.81 (d, 2H), 7.93 (d, 2H), 8.04 (s, 1H), 9.9 (bs, 1H), 10.9 (bs, 1H).

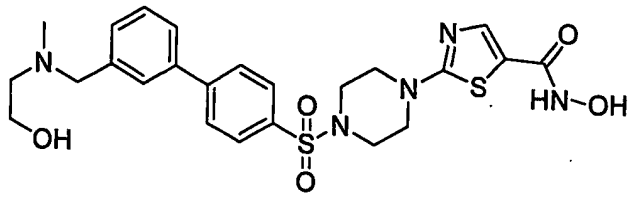
Example 310



2-(4-{4-[(3-((dimethylamino)methyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide

[00705] Floculant white solid, m/e = 508 ($M + H^+$), ^{1}HNMR (DMSO-d_6), δ: 2.62 (d, 6H), 3.10 (m, 4H), 3.55 (m, 4H), 4.33 (d, 2H), 7.36 (d, 1H), 7.65(bs, 1H), 7.72 (d, 2H), 7.83-7.87 (m, 3H), 9.6 (bs, 1H), 9.9 (bs, 1H).

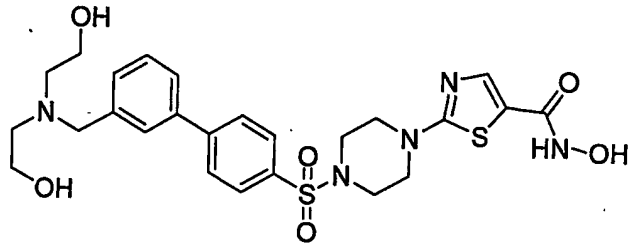
Example 311



2-{4-[3'-{[(2-hydroxyethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00706] ^{1}H NMR (DMSO-d_6, 400MHz), δ: 9.6 (brs, 1H, NH or OH), 7.97 (m, 3H, 3Ar-H), 7.87 (m, 3H, 3Ar-H), 7.60 (m, 3H, 3Ar-H), 4.46 (m, 1H, H-CH), 4.36 (m, 1H, H-CH), 3.59 (m, 2H, CH_2), 3.50 (m, 5H, $2CH_2$ & H-CH), 3.07 (m, 5H, $2CH_2$ & H-CH), 2.77 (s, 3H, N-CH_3), m/e = 532 ($M + H^+$).

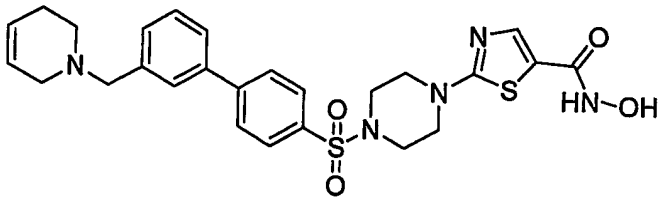
Example 312



2-{4-[3'-{[bis(2-hydroxyethyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00707] ^{1}H NMR (DMSO-d_6, 400MHz), δ; 10.9 (brs, 1H, NH or OH), 9.43 (brs, 1H, NH or OH), 7.98 (m, 3H, 3Ar-H), 7.88 (m, 3H, 3Ar-H), 7.61 (m, 3H, 3Ar-H), 5.4 (brs, 1H, OH or NH), 4.51 (s, 2H, CH_2), 3.79 (m, 4H, $2CH_2$), 3.59 (m, 4H, $2CH_2$), 3.32 (m, 4H, CH_2), 3.07 (m, 4H, $2CH_2$), m/e = 562 ($M + H^+$).

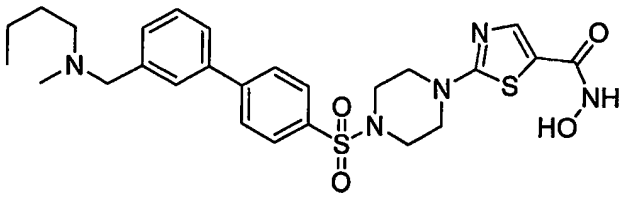
Example 313



2-{4-[3'-(3,6-dihydropyridin-1(2*H*)-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00708] ^{1}H NMR (DMSO-d_6, 400MHz), δ: 10.5 (brs, 1H, NH or OH), 10.3 (brs, 1H, NH or OH), 8.00-7.59 (m, 9H, 9Ar-H), 5.92 (m, 1H, =CH), 5.7 (m, 1H, =CH), 4.4 (s, 2H, CH_2), 3.59-3.48 (m, 6H, $3CH_2$), 3.07 (brs, 6H, $3CH_2$), 2.34 (m, 2H, CH_2), m/e = 540.3 ($M + H^+$).

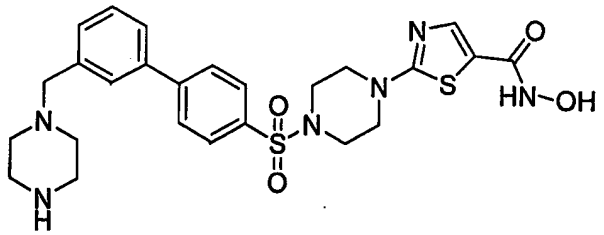
Example 314



2-{4-[3'-{[(butyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00709] ^{1}H NMR (DMSO-d_6, 400MHz), δ: 7.99-7.86 (m, 6H, 6Ar-H), 7.65-7.57 (m, 3H, 3Ar-H), 4.46 (m, 1H, benzylic CH), 4.29 (m, 1H, benzylic CH), 3.59 (brs, 4H, $2CH_2$), 3.44 (brs, 2H, CH_2), 3.07 (m, 4H, $2CH_2$), 2.7 (s, 3H, N-CH_3), 1.68 (m, 2H, CH2), 1.31 (m, 2H, CH_2), 0.9 (t, 3H, J = 8Hz, CH_3), m/e = 544.1 ($M + H^+$).

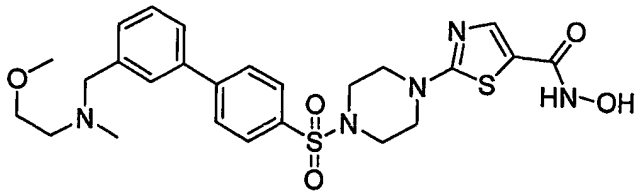
Example 315



2-{4-[3'-((piperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00710] ^{1}H NMR (DMSO-d_6, 400MHz), δ: 9.38 (brs, 2H, 2NH), 8.02 (d, 2H, J = 8Hz, 3Ar-H), 7.85 (t, 3H, 3Ar-H), 7.64-7.57 (m, 3H, 3Ar-H), 4.3 (brs, 1H, OH), 3.65-3.08 (m, 16H, $8CH_2$), m/e = 543 ($M + H^+$).

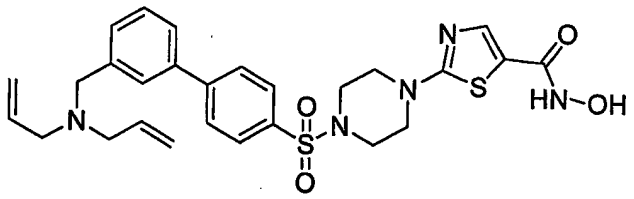
Example 316



2-{4-[3'-{[(2-methoxyethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00711] ^{1}H NMR (DMSO-d_6, 400MHz), δ: 10.5 (brs, 1H, OH or NH), 9.81 (brs, 1H, OH or NH), 7.99-7.58 (m, 6H, 6Ar-H), 7.64 – 7.58 (m, 3H, 3Ar-H), 4.1 (m, 1H, benzylic CH), 4.03 (m, 1H, benzylic CH), 3.61 (m, 2H, CH2), 3.65 (brs, 4H, $2CH_2$), 3.59-3.3 (m, 5H, OCH_3 & CH_2), 3.2 (brs, 4H, $2CH_2$), 2.76 (s, 3H, N-CH_3), m/e = 546.2 ($M + H^+$).

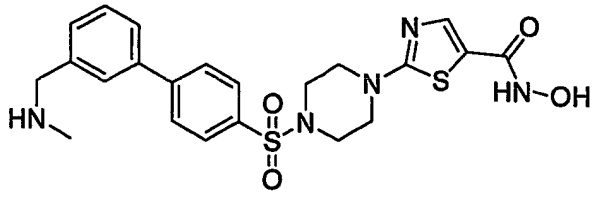
Example 317



2-{4-[3'-{[bis(3-propenyl))amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00712] ^{1}H NMR (DMSO, 400 MHz), δ: 10.80 (br s, 1H, -NH or –OH), 10. 22 (br s, 1H, -NH or –OH), 7.80-7.87 (m, 6H, 6 Ar-H), 7.67-7.61 (m, 3H, 3 Ar-H), 6.04-5.96 (m, 2H), 5.57-5.53 (m, 4H), 4.38 (br s, 2H), 3.73 (br s, 4H), 3.60 (br s, 4H, -CH2-CH2-), 3.08 (br s, 4H, -CH2-CH2-); m/e = 554.2 ($M + H^+$).

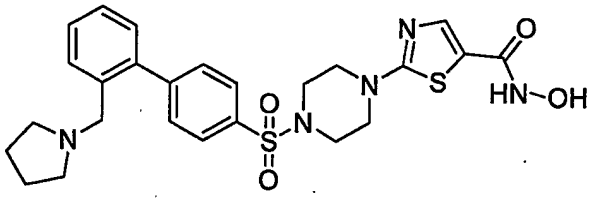
Example 318



2-{4-[3'-{[methylamino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00713] ^{1}H NMR (DMSO, 400 MHz), δ; 9.38 (br s, 1H, -NH or –OH), 9.14 (br s, 1H, -NH or –OH), 8.03-7.81 (m, 6H, 6Ar-H), 7.59 (d, 3H, 3 Ar-H), 4.20 (br s, 2H, -CH2-), 3.61 (d, 4H, -CH2-CH2-), 3.15 (d, 4H, -CH2-CH2-), 2.57 (br s, 3H, -CH3); m/e = 488.1 ($M + H^+$).

Example 321



2-{4-[2'-{pyrrolidin-1-ylmethyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide

[00714] ^{1}H NMR (CD_3OD, 200 MHz), δ: 7.97-7.58 (9H, m), 4.35 (2H, m), 3.71 (4H, m), 3.25 (4H, m), 3.21(4H, m), 1.87 (4H, m); MS (*m/e*) = 528 ($M+H^+$).

Biological Examples

Example A

In vitro fluorescent histone deacetylase assay

[00715] Assays were performed as in Part I. The following table shows the percent inhibition of HDAC produced by some of the examples of the present invention at a concentration of 100 μM.

Example Number	% inhibition HDAC @ 100 μM	Example Number	% inhibition HDAC @ 100 μM
201	294	238	100
203	293	239	98
204	300	295	98
209	297	246	98
205	285	306	99
202	299	305	99
210	288	243	99
207	298	294	98
211	298	242	98
299	299	244	98
		251	100
206	297	247	96
208	298	245	95
213	299	282	99
212	298	288	99
		284	100
248	296	285	100
215	292	300	96
218	295	252	96
217	296	289	99
220	297	287	99
216	300	286	99
249	285	261	95
214	298	260	99
219	299	296	100
221	300	298	98
222	300	291	99
274	300	253	94
223	299	254	100
224	300	292	100
225	298	293	100
226	298	297	99
268	299		
270	299	273	100
280	299	229	300
227	299	263	298
228	300		
271	300		
275	300		
250	299		
301	300	264	248
302	299	265	299
269	300	266	299
281	300	267	300
303	300	255	29
304	300	276	299
256	298	277	300
232	299	278	300
230	299	279	299
231	299	262	298
272	298	299	299
235	297		

Example Number	% inhibition HDAC @ 100 μM	Example Number	% inhibition HDAC @ 100 μM
234	292		
233	296		
237	299		
257	293		
258	295	283	300
259	299	290	299
236	298		
241	298		
240	300		
307	300	320	290
308	300	321	297
309	300	322	298
310	300	323	300
311	300	324	298
312	299	325	299
313	298	326	299
314	298	327	299
315	300	328	299
316	299	329	299
317	298	330	299
318	300	331	291
319	299	332	295

[00716] In some assays recombinant HDAC8 (Biomol) was used as the source of the enzyme activity; here the final substrate concentration was 250 μM, the final concentration of HDAC8 was 0.02 Units/μL and the reaction was allowed to proceed at 37 °C for 1 h before stopping. For all curves, IC_{50} values were calculated with the GraFit curve-fitting program (Erithacus, Horley, Surrey, UK).

Example B

Whole Cell Cytotoxicity Assay:Sulforhodamine B

[00717] Assays were performed as in Part I. The following table shows the percent inhibition of MCF7 cell growth produced by some of the examples of the present invention at a concentration of 100 μM.

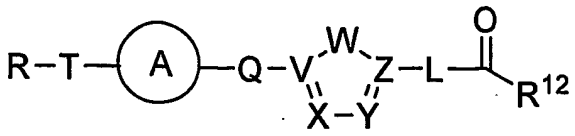
Example Number	% inhibition MCF7 cells @ 100 μM	Example Number	% inhibition MCF7 cells @ 100 μM
201	95	238	97.8
203	95.3	239	97.9
204	95.4	295	96.8
209	97.7	246	77.3
205	97.9	306	82.3
202	98.3	305	93
210	97.8	243	91

207	83.3	294	90.6
211	96.7	242	90
		244	91.7
		251	97
206	95.1	247	90.2
208	90.1	245	78.7
213	98.9	282	92.7
212	95.5	288	93.8
		284	96.7
248	89.4	285	97.5
215	88.5	300	96.8
218	96.6	252	97.3
217	97.8	289	98.3
220	97.9	287	97.7
216	90.9	286	97.8
249	95.4	261	92.2
214	89.8	260	92.1
219	76.5	296	85.6
221	97.1	298	92.2
222	98	291	94.6
274	97.3	253	89.9
223	96.7	254	97.1
224	95.3	292	88.8
225	90.1	293	92.7
226	90	297	83.9
268	84.7		
270	83.6	273	96.7
280	97.9	229	98.5
227	88.5	263	93.3
228	92.7		
271	97.2		
275	98.6		
250	98.3		
301	98.1	264	87
302	84	265	95
269	87.7	266	97
281	97.1	267	98
303	97.5	255	0
304	97.6	276	98
256	96.9	277	98
232	98.1	278	99
230	97.9	279	98
231	97.7	262	75
272	84.5	299	96
235	97.9		
234	97.7		
233	98.4		
237	98		
257	68.6		
258	97.6	283	98
259	98.9	290	98
236	98.2		
241	98.1		
240	99.1		
307	99	320	92
308	99	321	95

309	83	322	99
310	98	323	100
311	98	324	96
312	85	325	98
313	92	326	98
314	97	327	92
315	95	328	96
316	97	329	97
317	66	330	91
318	86	331	76
319	89	332	30

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

wherein:

R is selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkyl and substituted alkyl;

R^{12} is selected from the group consisting of $-NR^{14}OH$, -OH, $-NR^{14}R^{15}$, $-OR^{14}$, $-(C_1-C_6)$alkylene-SR^{14}, $-(C_1-C_6)$alkylene-OR^{14}, $-(C_1-C_6)$alkylene-$NR^{14}R^{15}$, $-CF_3$;

where R^{14}, R^{15} are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)substituted alkyl, aryl, substituted aryl and where R^{14} and R^{15} together with the nitrogen atom bound thereto form a heterocyclic or substituted heterocyclic ring;

V, W, X, Y, and Z form a 5-membered heteroaryl where W, X, and Y independently form $=C(R^{11})-$, -N=, $-N(R^{14})-$, -O-, -S-, -S(O)-, and/or $-S(O)_2-$, and V and Z independently form $=C(R^{14})-$ and/or, >N- where R^{14} is as defined above and provided that at least one of V, W, X, Y and Z is $=C(R^{14})-$ and that V, W, X, Y, and Z do not form a thienyl;

the ring defined by A above is selected from the group consisting of cycloalkylene, substituted cycloalkylene, hetrocyclene, substituted heterocyclene, arylene and heteroarylene;

T is selected from the group consisting of $-SO_2-[(C_1-C_3)\text{alkylene}]_p-$, $-[(C_1-C_3)\text{alkylene}]_p-SO_2-$, $-NR^{16}SO_2-[(C_1-C_3)\text{alkylene}]_p-$, $-SO_2NR^{16}-[(C_1-$

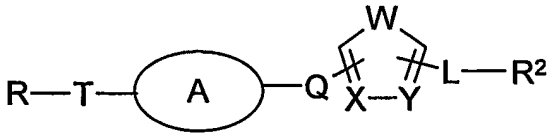
C_3)alkylene]$_p$-, -C(O)-[(C_1-C_3)alkylene]$_p$-, -[(C_1-C_3)alkylene]$_p$-C(O)-, -NR^{16}C(O)-[(C_1-C_3)alkylene]$_p$-, -C(O)NR^{16}-[(C_1-C_3)alkylene]$_p$-, -N(R^{16})-[(C_1-C_3)alkylene]$_p$ and (C_1-C_3)alkylene where *p* is zero or one and R^1 is hydrogen, alkyl, aryl or heteroaryl;

Q is selected from the group consisting of a covalent bond, (C_1-C_3)alkylene, -NR^1C(O)NR^1-, -NR^1C(O)-, -C(O)NR^1-, -(C_1-C_3-alkylene)$_p$$NR^1$- and -$NR^1$-($C_1$-$C_3$-alkylene)$_p$ where R^1 is hydrogen or alkyl and *p* is zero or one, provided that Q is not attached to X, Y or W when W is -O-, -S-, -S(O)-, -$S(O)_2$- and further provided that when Q is -NR^1- then Q is attached to a carbon atom of the ring defined by A above;

L is selected from the group consisting of a covalent bond, alkylene (C_1-C_4), substituted alkylene (C_1-C_4), alkenylene (C_2-C_4), and substituted alkenylene (C_2-C_4), cycloalkylene (C_3-C_8), and substituted cycloalkylene (C_3-C_8);

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 having the formula **Ia**:



Ia

wherein:

R is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of –C(O)NR^4R^5, -N(H)C(O)R^6 -C(O)(C_1-C_6)alkenylSR^6, NR^7C(O)N(OH)R^6, NR^7C(O)(C_1-C_6)alkenylSR^6;

where R^4 and R^5 are independently selected from the group consisting of hydrogen, hydroxyl, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, and aminoaryl provided that both R^4 and R^5 are not hydroxyl;

R^6 is independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkylcarbonyl, aryl(C_1-C_6)alkyl, (C_1-C_6)alkylpyrazinyl, pyridinone, pyrrolidinone and methylimidazolyl; and

R^7 is independently selected from the group consisting of hydrogen, and (C_1-C_6)alkyl;

the ring defined by **A** above is selected from the group consisting of cycloalkylene, substituted cycloalkylene, heterocyclene and substituted heterocyclene;

T is selected from the group consisting of a bond, $-SO_2-[(C_1-C_3)\text{alkylene}]_p-$, $-NR^1SO_2-[(C_1-C_3)\text{alkylene}]_p-$, $-SO_2NR^1-[(C_1-C_3)\text{alkylene}]_p$, $-C(O)-[(C_1-C_3)\text{alkylene}]_p-$, $-NR^1C(O)-[(C_1-C_3)\text{alkylene}]_p-$, $-C(O)NR^1-[(C_1-C_3)\text{alkylene}]_p-$, and (C_1-C_3)alkylene where *p* is zero or one and R^1 is hydrogen or alkyl;

W is selected from the group consisting of -O-, -S-, -S(O)-, $-S(O)_2-$ and $-NR^1-$ where R^1 is as defined above;

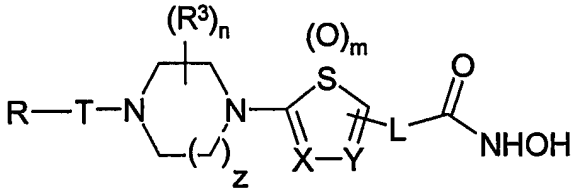
X and Y is selected from the group consisting of >CH and >N such that the 5 membered ring defined by W, X, Y and the two >CH groups is a heteroaryl ring, with the proviso that said heteroaryl ring is not a thienyl;

Q is selected from the group consisting of a covalent bond, (C_1-C_3)alkylene, $-NR^1C(O)NR^1-$, $-NR^1C(O)-$, $-C(O)NR^1-$, $-(C_1-C_3\text{-alkylene})_pNR^1-$ and $-NR^1-(C_1-C_3\text{-alkylene})_p$ where R^1 is hydrogen or alkyl and *p* is zero or one, provided that Q is not attached to X, Y or W when W is -O-, -S-, -S(O)-, $-S(O)_2-$ and further provided that when Q is $-NR^1-$ then Q is attached to a carbon atom of the ring defined by A above;

L is selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, and substituted alkenylene, cycloalkylene, and substituted cycloalkylene, provided that L is attached to a carbon atom of the 5 membered heteroaryl group;

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

3. The compound according to Claim 2, wherein said compound is represented by formula II:



II

wherein:

R is selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkyl and substituted alkyl;

X, and Y independently form $=C(R^{11})-$, $-N=$, $-N(R^{14})-$, $-O-$, $-S-$, $-S(O)-$, and/or $-S(O)_2-$, and V and Z independently form $=C(R^{14})-$ and/or, $>N-$ where R^{14} is as defined above and provided that at least one of V, W, X, Y and Z is $=C(R^{14})-$, and further provided that V, W, X, Y and Z do not form a thienyl;

T is selected from the group consisting of $-SO_2-[(C_1-C_3)alkylene]_p-$, $-[(C_1-C_3)alkylene]_p-SO_2-$, $-NR^{16}SO_2-[(C_1-C_3)alkylene]_p-$, $-SO_2NR^{16}-[(C_1-C_3)alkylene]_p-$, $-C(O)-[(C_1-C_3)alkylene]_p-$, $-[(C_1-C_3)alkylene]_p-C(O)-$, $-NR^{16}C(O)-[(C_1-C_3)alkylene]_p-$, $-C(O)NR^{16}-[(C_1-C_3)alkylene]_p-$, $-N(R^{16})-[(C_1-C_3)alkylene]_p$ and $(C_1-C_3)alkylene$ where *p* is zero or one and R^1 is hydrogen, alkyl, aryl or heteroaryl;

L is selected from the group consisting of a covalent bond, alkylene (C_1-C_4), substituted alkylene (C_1-C_4), alkenylene (C_2-C_4), and substituted alkenylene (C_2-C_4), cycloalkylene (C_3-C_8), and substituted cycloalkylene (C_3-C_8);

each R^3 is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

m, *n* and *z*, are independently integers equal to zero, one or two; and

tautomers, isomers, prodrugs, and pharmaceutically acceptable salts thereof.

4. The compound according to Claim 1, wherein R is aryl or substituted aryl.

5. The compound according to Claim 1, wherein R is selcted from the group consisting of phenyl, naphthyl, 3,4-dimethoxyphenyl, 4-trifluoromethoxyphenyl, 4-methylphenyl, 4-triflurormethylphenyl, 4-nitrophenyl, 4-acetylphenyl, thiophen-2-yl, biphenyl, 5-(N,N-dimethylamino)-naphthalenyl, 4-fluorophenyl, methyl, benzyl, 2-hydroxyethyl, 2-aminoethyl, and 2-phenylethyl.

6. The compound according to Claim 1, wherein R^3 is alkyl and *n* is selected from the group consisting of one and zero.

7. The compound according to Claim 1, wherein *m* is zero.

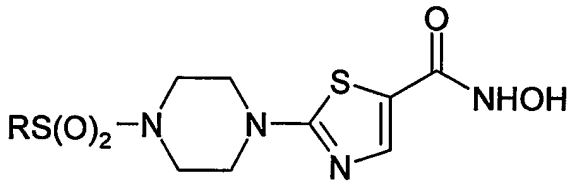
8. The compound according to Claim 1, wherein Q is a covalent bond and the ring defined by A above is piperidinyl.

9. The compound according to Claim 1, wherein X is nitrogen and Y is CH.

10. The compound according to Claim 1, wherein T is selected from the group consisting of a bond, $-SO_2-$, and $-SO_2NH-$.

11. The compound according to Claim 1, wherein L is selected from the group consisting of a covalent bond, an alkenylene group, and a cycloalkylene.

12. A compound of Claim 3, having the formula XI:



XI

wherein:

R is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, amino, substituted amino, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

or tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof

with the proviso that R is not 4-aminophenyl.

13. The compound of Claim 12 wherein R is aryl or substituted aryl.

14. The compound of Claim 13 wherein R is selected from the group consisting of:

phenyl, napthyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-trifluoro-methoxyphenyl, 2-triflurorомethylphenyl, 3-triflurorомethylphenyl, 4-tri-fluoromethylphenyl, 4-nitrophenyl, 4-acetylphenyl, 4-[(N-morpholino)-methyl]phenyl, 4-[(N-pyrrolidinyl)methyl]phenyl, 4-(N,N-dimethylamino-methyl)phenyl, 5-(N,N-dimethylamino)naphthyl, 4-pyrrolind-1-ylphenyl, 4-acetamidophenyl, 4-methyl-2,3-dihydrobenzisoxazinyl, 2,3-dihydro-benzofuran-5-yl, 2,1,3-benzothiadiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-chlorophenyl, 2-chloro-6-methylphenyl, 3-chloro-2,5-dimethylphenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chlorophenyl, 3-cyanophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-fluorophenyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 5-fluoro-2-methylphenyl, 4-methyl-sulfonylphenyl, 2-methylphenyl, 3-methylphenyl, 3-hydroxymethylphenyl, 3-(N,N-dimethylaminomethyl)phenyl, 3-(pyrrolidin-1-yl)methylphenyl, 4-ethylphenyl,4-methylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-*iso*-propylphenyl, 4-*n*-propylphenyl, *t*-butylphenyl, (4-pyrazol-1-yl)phenyl, 3-biphenyl, 4-biphenyl, 4-(3-N,N-dimethylaminomethylphenyl)phenyl, 4-(3-N,N-dimethylaminophenyl)phenyl, 4-[(3-pyrrolind-N-ylmethyl)-phenyl]phenyl, 4-[(N-morpholinocarbonyl)phenyl]phenyl, 4-(N,N-dimethyl-aminocarbonylphenyl)phenyl, 4-(4-fluorophenyl)phenyl, 4-(pyrid-4-yl)phenyl, 4-(3-chlorophenyl)phenyl, 4-(2-chlorophenyl)phenyl, 4-(3-fluorophenyl)-phenyl, 4-(2-furanyl)phenyl, 4-[2-(pyrrrolidin-N-ylmethyl)thien-3-yl]phenyl, 4-[5-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(4-methylpiperidin-1-yl)phenyl]phenyl, 4-[(3-(N-methyl-N-{2-N,N-dimethyleth-1-yl}aminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-ethylaminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-isopropyl}aminomethyl)phenyl]phenyl, 4-(methylsulfonamidophenyl)phenyl, 4-[1,3-(benzodioxol-5-yl)]phenyl, 4-(pyrimidin-5-yl)phenyl, 2-(2-methyl-

thiopyrimidin-4-yl)thien-5-yl, 4-[4-(acetamidophenyl)]phenyl, 4-(2-N,N-dimethylaminothien-3-yl)phenyl, and 4-(pyrid-3-yl)phenyl.

15. The compound according to Claim 12 wherein R is heteroaryl or substituted heteroaryl.

16. The compound according to Claim 15 wherein R is selected from the group consisting of thien-2yl, pyrid-2-yl, pyrid-3-yl, and benzothio-furan-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(4-morpholino)-pyrid-5-yl, and 2-phenoxypyrid-5-yl.

17. The compound according to Claim 12 wherein R is alkyl or substituted alkyl.

18. The compound according to Claim 17 wherein R is selected from the group consisting *n*-butyl, benzyl, and 2-phenylethyl.

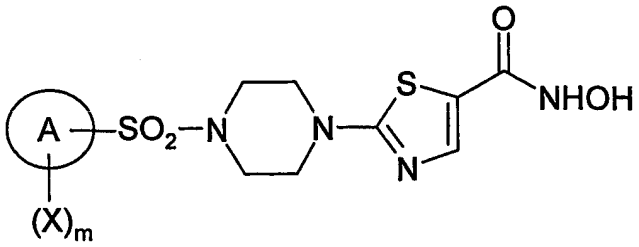
19. The compound according to Claim 12 wherein R is alkenyl or substituted alkenyl.

20. The compound according to Claim 19 wherein R is *trans*-2-phenylethen-1-yl.

21. The compound according to Claim 12 wherein R is selected from the group consisting of amino, substituted amino, dimethylamino, and a heterocyclic group.

22. The compound according to Claim 21 wherein R is 1-methyl-imidazol-4-yl.

23. A compound of claim 3 having the formula XII:



XII

wherein:

A is selected from the group consisting of aryl and heteroaryl;

X is selected from the group consisting of acyl, acylamino, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, aminoacyl, aryloxy, substituted aryloxy, cyano, halo, heterocyclic, substituted heterocyclic, nitro, thioalkyl, substituted thioalkyl, and R^2-$S(O)_2(NH)_n$- where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

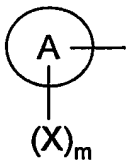
m is zero, one, two or three; and

n is zero or one;

or tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof,

with the proviso that -A-$(X)_m$ is not 4-aminophenyl.

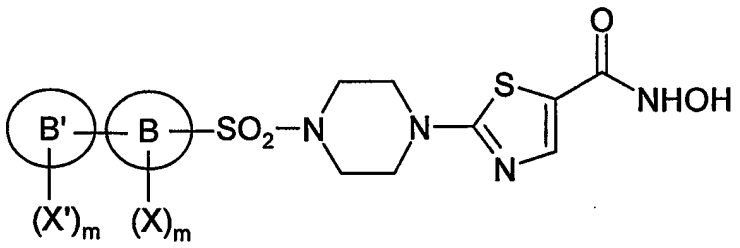
24. The compound according to Claim 23 wherein the substituent defined by



is selected from the group consisting of phenyl, naphthyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-trifluoromethoxyphenyl, 2-triflurormethylphenyl, 3-triflurormethylphenyl, 4-triflurormethylphenyl, 4-nitrophenyl, 4-acetylphenyl, 4-[(N-morpholino)methyl]phenyl, 4-[(N-pyrrolidinyl)methyl]phenyl, 4-(N,N-dimethylaminomethyl)phenyl, 5-(N,N-dimethylamino)naphthyl, 4-pyrrolind-1-ylphenyl, 4-acetamidophenyl, 4-

methyl-2,3-dihydrobenzisoxazinyl, 2,3-dihydrobenzofuran-5-yl, 2,1,3-benzothiadiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-chlorophenyl, 2-chloro-6-methylphenyl, 3-chloro-2,5-dimethylphenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chlorophenyl, 3-cyanophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-fluorophenyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methylphenyl, 5-fluoro-2-methylphenyl, 4-methylsulfonylphenyl, 2-methylphenyl, 3-methylphenyl, 3-hydroxymethyl-phenyl, 3-(N,N-dimethylaminomethyl)phenyl, 3-(pyrrolidin-1-yl)methylphenyl, 4-ethylphenyl,4-methylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 4-*iso*-propylphenyl, 4-*n*-propylphenyl, *t*-butylphenyl, thien-2-yl, pyrid-2-yl, pyrid-3-yl, benzothiofuran-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(4-morpholino)pyrid-5-yl, and 2-phenoxypyrid-5-yl.

25. A compound of claim 3 having the formula XIII:



XIII

wherein:

B and B′ are independently selected from the group consisting of aryl and heteroaryl;

X and X′ are independently selected from the group consisting of acyl, acylamino, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, aminoacyl, aryloxy, substituted aryloxy, cyano, halo, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, nitro, thioalkyl, substituted thioalkyl, R^2-$S(O)_2(NH)_n$-, where R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, and

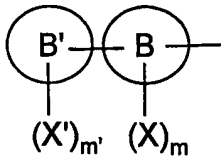
m is zero, one, two or three;

m' is zero, one or two; and

n is zero or one

or tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

26. The compound according to Claim 25 wherein the substituent defined by the formula:



is selected from the group consisting of (4-pyrazol-1-yl)phenyl, 3-biphenyl, 4-bi-phenyl, 4-(3-N,N-dimethylaminomethylphenyl)phenyl, 4-(3-N,N-dimethyl-aminophenyl)phenyl, 4-[(3-pyrrolind-N-ylmethyl)phenyl]phenyl, 4-[(N-morpholinocarbonyl)phenyl]phenyl, 4-(N,N-dimethylaminocarbonyl-phenyl)phenyl, 4-(4-fluorophenyl)phenyl, 4-(pyrid-4-yl)phenyl, 4-(3-chloro-phenyl)phenyl, 4-(2-chlorophenyl)phenyl, 4-(3-fluorophenyl)phenyl, 4-(2-furanyl)phenyl, 4-[2-(pyrrrolidin-N-ylmethyl)thien-3-yl]phenyl, 4-[5-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(pyrrrolidin-N-ylmethyl)thien-2-yl]phenyl, 4-[3-(4-methylpiperidin-1-yl)phenyl]phenyl, 4-[(3-(N-methyl-N-{2-N,N-dimethyleth-1-yl}aminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-ethylaminomethyl)phenyl]phenyl, 4-[(3-(N-methyl-N-isopropyl}aminomethyl)-henyl]phenyl, 4-(methylsulfonamidophenyl)phenyl, 4-[1,3-(benzodioxol-5-yl)]phenyl, 4-(pyrimidin-5-yl)phenyl, 2-(2-methylthiopyrimidin-4-yl)thien-5-yl, 4-[4-(acetamidophenyl)]phenyl, 4-(2-N,N-dimethylaminothien-3-yl)phenyl, and 4-(pyrid-3-yl)phenyl.

27. A compound selected from the group consisting of:

1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl) piperazine;

1-(2-naphthylsulfonyl)-4-(5-hydroxyaminocarbonylthiazol-2-yl)-1,4-diazepane;

1-(2-naphthylsulfonyl)-4-(4-hydroxyaminocarbonylthiazol-2-yl)

piperazine;

1-(2-naphthylsulfonyl)-4-[(5-(2-hydroxyaminocarbonylethen-1(Z)-yl-thiazol-2yl) piperazine;

4-(2-naphthylsulfonylamino)-1-[(5-(2-hydroxyaminocarbonyl-thiazol-2-yl)-piperadine;

2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4 toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-(4-methyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4- Benzyl -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-(2-hydroxyethyl) -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-(2-aminoethyl) -piperazin-1-yl)-thiazole-5-carboxylic acid hydroxyamide;

2-(4-phenylethyl -piperazin-1-yl)-thiazole-5-carboxylic acid

hydroxyamide;

2-(4-acetyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide;

2-(4-benzoyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide;

2-(4-phenylacetyl-piperazin-1-yl)-thiazole-5-carboxylic acid hydroxamide;

N-(2-naphthylsulfonyl)-N'-{2-[5-(N-hydroxycarboxamido)]thiazolyl}-piperazine;

2-[4-(naphtha-2-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-toluene-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-dimethoxy-benzene sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-acetyl-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-fluoro-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-pyrolidinylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(thiophene-2-benzenesulfonyl)-piperazin-1-yl]-thiazole-5-

carboxylic acid hydroxyamide;

2-[4-(N-methyl-2,3-dihydrobenzisoxazinylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(trans-2-phenylethanelsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-dichlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(N,N-dimethylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-methylsufonylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(pyridine-3-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-[(dimethylamino)methyl]-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-n-propylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,5-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-t-butylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(benzylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid

hydroxyamide;

2-[4-(4'-N,N-dimethylcarboxamido-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4'-methylsulfonylamino-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-((dimethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,5-dimethylisoxazolesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-({4-morpholino}-3-pyridylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3'-(dimethylamino)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(pyrrolidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-dimethylaminophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-dimethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4'-(morpholin-4-ylcarbonyl)-1,1'-biphenylsulfonyl)piperazin-1-yl]-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(2-((dimethylamino)-methyl)thien-3-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-fluoro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-chloro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-chloro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[4-(pyridin-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-methyl-5-fluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2'-chloro-1,1'-biphenyl-4-yl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(2-furyl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-fluoro-2-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-fluoro-4-methylphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-methyl-6-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2,5-dimethyl-4-chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2,1,3-benzothiadiazole-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-benzothiphenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2,3-dihydrobenzofuransulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,4-benzodioxansulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-biphenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-phenoxypyridine-5-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(2-{2-methylthiopyrimidine-4-yl}-5-thiophenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-(4-[4-{(2-(pyrrolidin-1-ylmethyl)-thien-3-yl)phenylsulfonyl}]-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(5-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-((4-methylpiperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(2-(dimethylamino)ethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3,5-difluorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-thien-2-yl]phenylsulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-[isopropyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-[ethyl(methyl)amino]methyl]-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-fluoro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(1,3-benzodioxol-5-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(n-butylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(chlorophenylsulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(5-bromothien-2-yl)sulfonyl]piperazin-1-yl}-N-hydroxy-1,3-thiazole-5-carboxamide;

2-{4-[(4'-chloro-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-methoxy-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-(2,2-dimethylpropyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4-thien-2-ylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxamide;

2-(4-{[4-(1-(2,2-dimethylprop-oxycarbonyl)-1H-pyrrol-2-yl)phenyl]-sulfonyl}-piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(1H-pyrrol-2-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(piperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(4-methylpiperidin-1-ylmethyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-(hexahydroazepin-1-ylmethyl)-1,1'-biphenylsulfonyl]-piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-((diethylamino)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(3'-((methyl(3-propenyl)amino)methyl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(3-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{5-[3-(pyrrolidin-1-ylmethyl)phenyl]thiophene-2-sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-pyrzaol-1-yl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{1-methylimidazol-4-yl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-methoxyphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-{3-trifluoromethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{N,N-dimethylaminomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{N-morpholinomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-{N-pyrrolidinylmethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-phenethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-ethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-hydroxymethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-pyrrolidin-1-ylmethylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-pyrimid-5-ylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4'-(acetamidophenyl)-phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-pyridylphenyl-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-{N,N-dimethylaminomethylphenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-methoxymethylbenzenesulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(4-acetamido-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-[4-(3-cyanophenyl}-4-sulfonyl)-piperazin-1-yl]-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2-chloro-5-methoxyphenyl)sulfonyl]piperazin-1-yl}--1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[3-(difluoromethoxy)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(4-methyl-3-nitrophenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2,5-dimethoxyphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(2,5-dimethylphenyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[2-(pyrrolidin-1-ylmethyl)-4-methylphenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[3-fluoro-4-(pyrrolidin-1-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(piperidin-1-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{[4-(morpholin-4-yl)phenyl]sulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[(trifluoromethyl)sulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[ethylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[*N*-acetylamino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{methoxymethyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[4-(2-(pyrrolidin-1-ylmethyl)-thien-4-yl)phenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[3-((dimethylamino)-methyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(4-(pyrrolidin-1-ylmethyl)-2-furyl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-(4-{4-[(3-((dimethylamino)methyl)-thien-2-yl]phenylsulfonyl}piperazin-1-yl)-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(2-hydroxyethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[bis(2-hydroxyethyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-(3,6-dihydropyridin-1(2*H*)-ylmethyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(butyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-((piperazin-1-yl)methyl)-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[(2-methoxyethyl)(methyl)amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[bis(3-propenyl))amino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[3'-{[methylamino]methyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

2-{4-[2'-{pyrrolidin-1-ylmethyl}-1,1'-biphenylsulfonyl]piperazin-1-yl}-1,3-thiazole-5-carboxylic acid hydroxyamide;

and tautomers, isomers, prodrugs and pharmaceutically acceptable salts thereof.

28. A pharmaceutical composition comprising an effective amount of one or more compounds according to Claim 1, a pharmaceutically inert carrier, and, optionally, at least one anti-cancer agent.

29. The pharmaceutical composition of Claim 28, wherein the anti-cancer agent is selected from platinum coordination compounds, taxane compounds, topoisomerase I inhibitors, topoisomerase II inhibitors, anti-tumour vinca alkaloids, anti-tumour nucleoside derivatives, alkylating agents, anti-tumour

anthracycline derivatives, HER2 antibodies, estrogen receptor antagonists, selective estrogen receptor modulators, aromatase inhibitors, retinoids, retinoic acid metabolism blocking agents (RAMBA), DNA methyl transferase inhibitors, kinase inhibitors, farnesyltransferase inhibitors, and other HDAC inhibitors.

30. The pharmaceutical composition of Claim 29, wherein the anti-cancer agent is selected from carboplatin, oxalyplatin, paclitaxel, docetaxel, irinotecan, topotecan, etoposide, teniposide, vinblastine, vincristine, vinorelbine, 5-fluorouracil, gemcitabine, capecitabine, cyclophosphamide, chlorambucil, carmustine, lomustine, daunorubicin, doxorubicin, darubicin, mitoxantrone, trastuzuma, tamoxifen, toremifene, droloxifene, faslodex, raloxifene, exemestane, anastrozole, letrazole, vorozole, vitamin D, accutane, azacytidine, flavoperidol, imatinib mesylate, and gefitinib.

31. A method for inhibiting a proliferative disorder in a mammalian patient which method comprises administering to said patient a pharmaceutical composition according to Claim 28.

32. A method for inhibiting a proliferative disorder in a mammalian patient which method comprises administering to said patient a pharmaceutical composition according to Claim 29.